VOLUME 43 NUMBER 2

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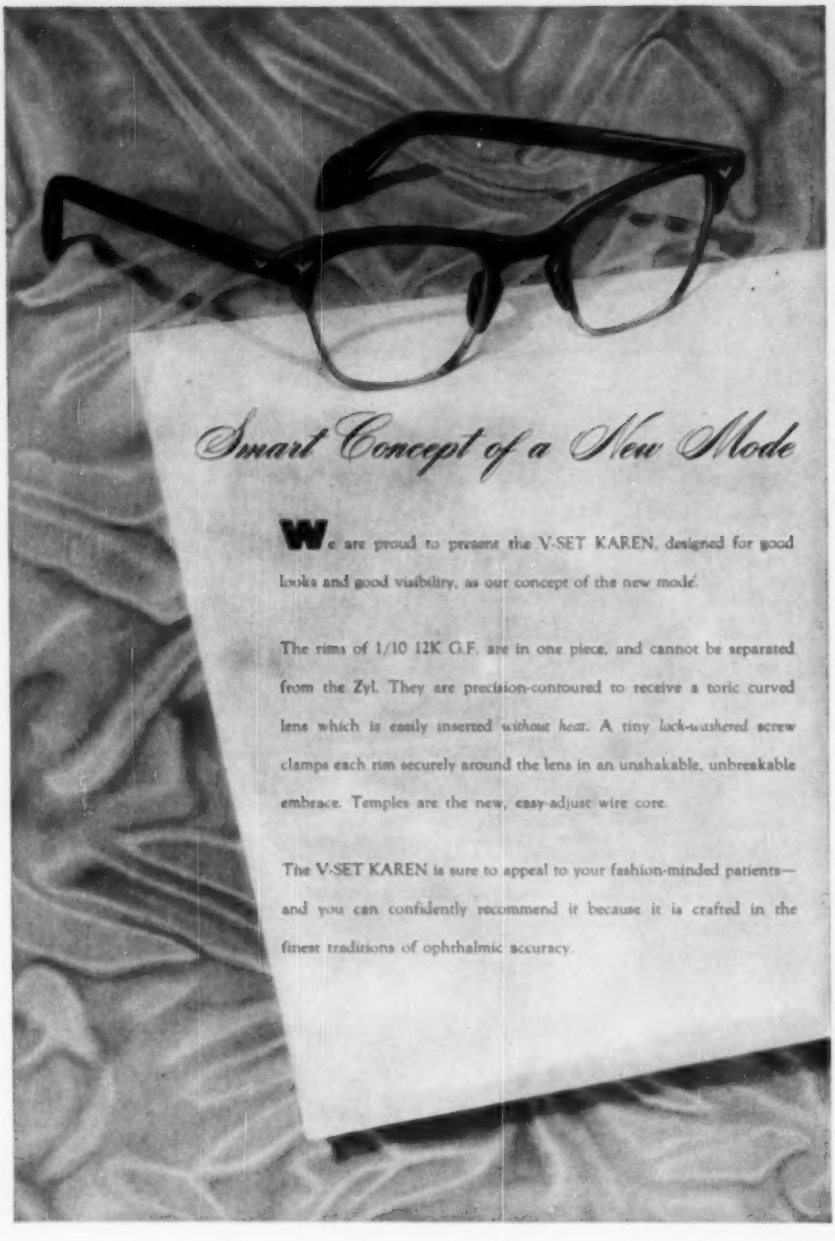

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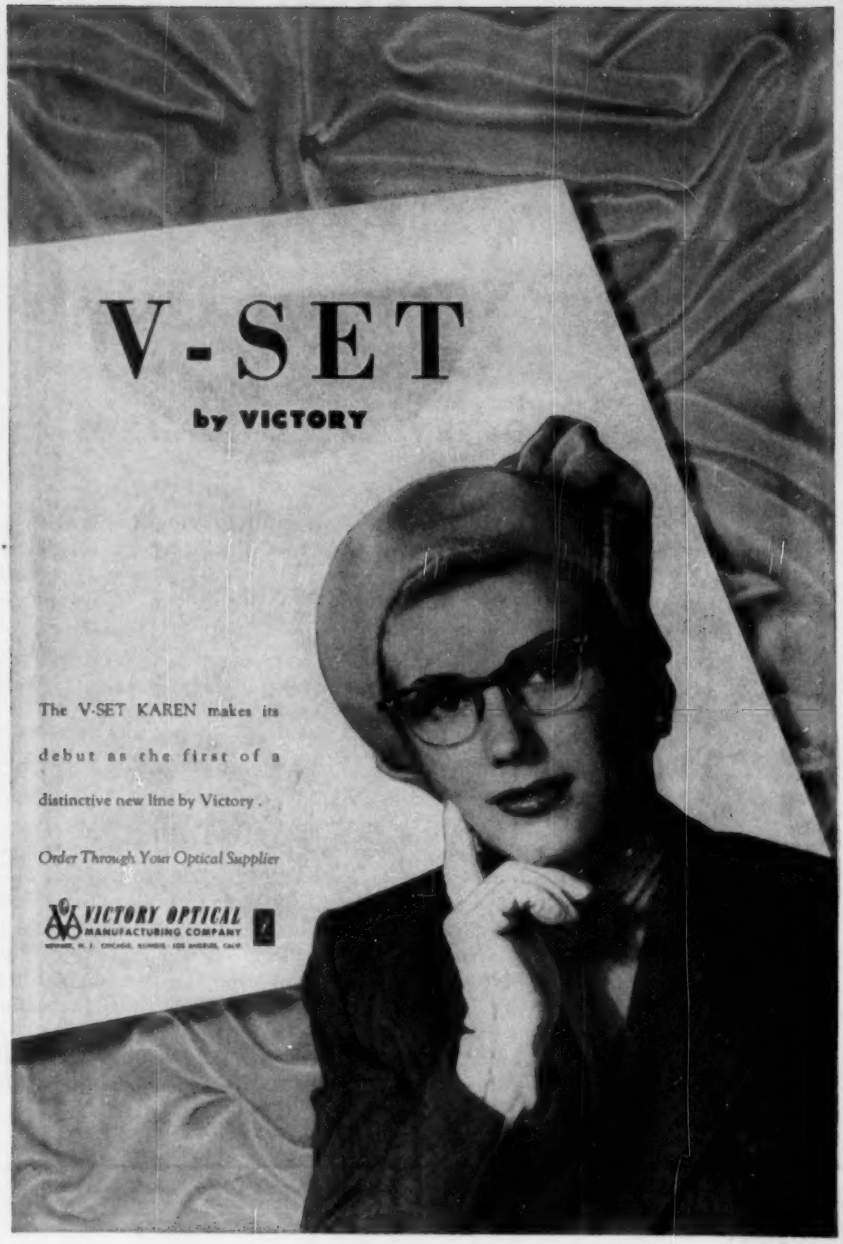
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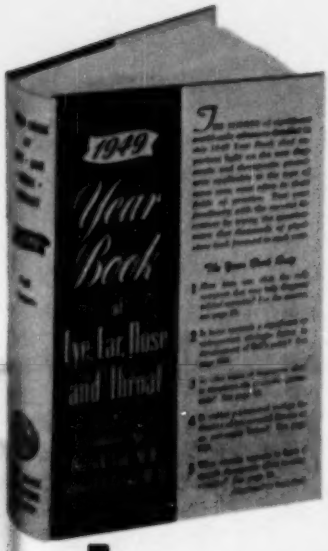

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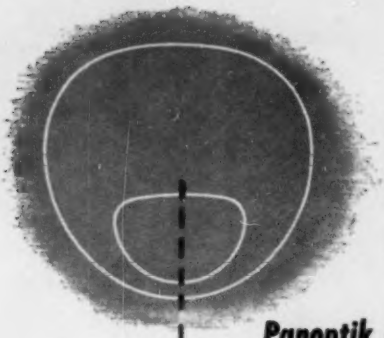

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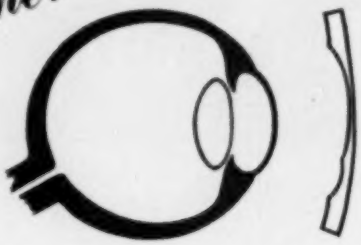

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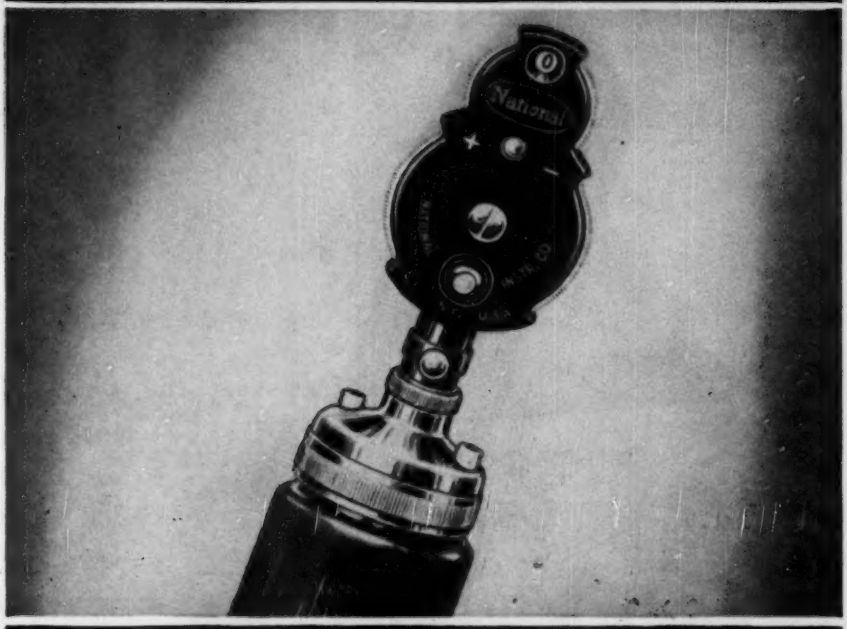

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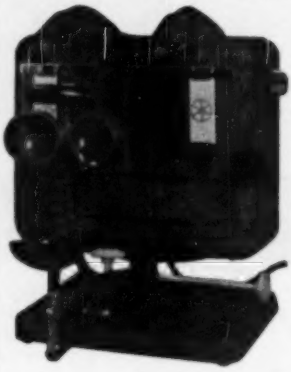

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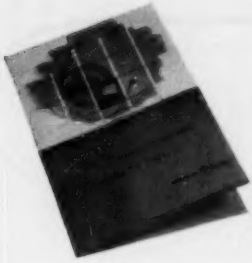

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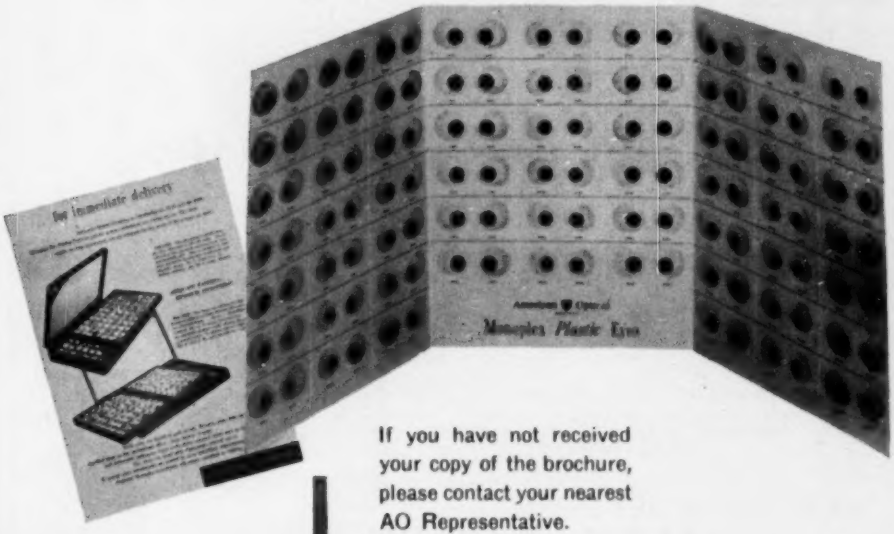

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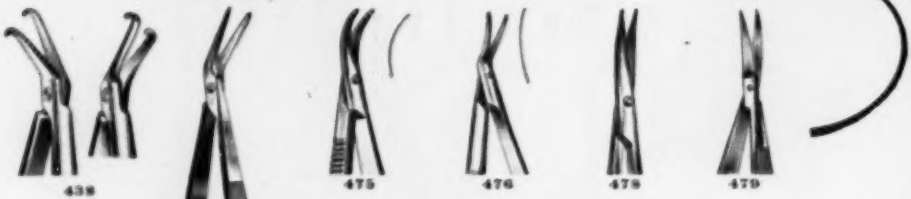

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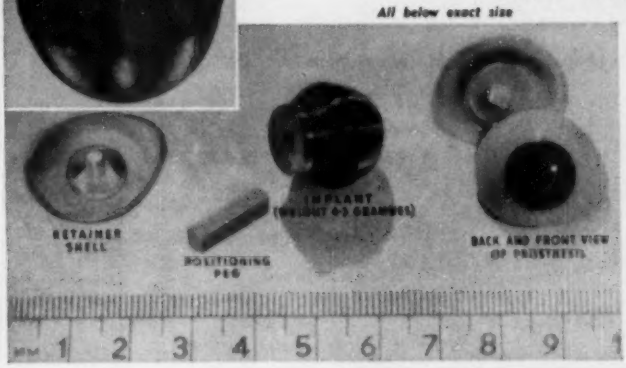
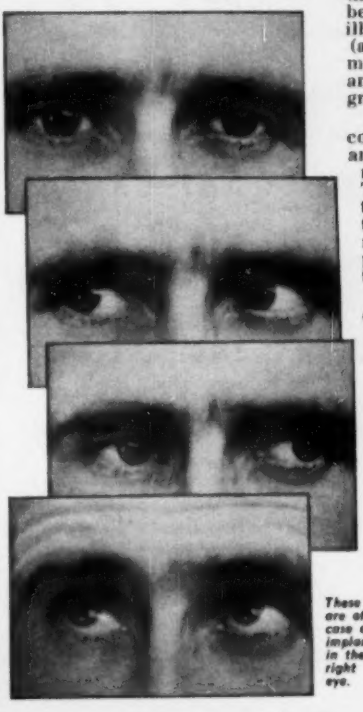


The latest Cutler Implant for use in enucleations, re-implantations and evisceroenucleations is described in an article by Dr. Norman Cutler in the February, 1949, issue of the American Journal of Ophthalmology in which is mentioned the objectives to be strived for in an ideal implant and prosthesis.

These are (1) wide range of movement, (2) instantaneous movement over the short ranges, (3) absence of sinking of the upper lid, and (4) absence of sagging of the lower lid, and he suggests that these objects have been attained in the latest type. Hamblin's model illustrated herewith is made entirely of Tantalum (a completely inert metal) thereby overcoming the many disadvantages of one made partly of Plastic and partly of Tantalum. The total weight is 4.3 grammes.



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ARCHIVES OF OPHTHALMOLOGY

VOLUME 43 FEBRUARY 1950 NUMBER 2

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OCCLUSION OF THE CENTRAL RETINAL ARTERY FOLLOWING ANESTHESIA

ISADORE GIVNER, M.D.
AND
NORMAN JAFFE, M.D.
NEW YORK

WHEN a coincidence is duplicated, one wonders whether the sum total of the circumstances do not have a causal relation rather than constitute an unrelated, chance happening.

REPORT OF CASES

CASE 1.—On April 1, 1947, S. L., a man in his late fifties, was operated on for carcinoma of the head of the pancreas. Cyclopropane-oxygen-ether anesthesia was administered from 8:05 to 12:30 a.m., and cholecystojejunostomy was performed. The patient was in shock but recovered well. At 5 p.m. the same day he complained of blurred vision in the right eye.

On April 2 ophthalmologic examination disclosed an abrasion of the right cornea, extending over half the surface. Examination of the fundus disclosed closure of the central retinal artery with a typical cherry red spot in the macula. The cornea healed; the vision never returned, and the impression was that of an unusual coincidence of abrasion of the cornea and closure of the central retinal artery on the basis of vascular disease, possibly endarteritic, although embolism could not definitely be ruled out.

CASE 2.—On March 9, 1948, P. B., a woman aged 33, had a ureterostomy. Mild shock occurred during the operation, which was performed with the patient under cyclopropane-oxygen-ether anesthesia and lasted from 9:15 to 10:40 a.m. The patient mentioned to the anesthetist that he was pressing on her right eye. This was the last statement she made before going under the anesthetic. At 3:15 p.m. she complained of not being able to see with the right eye.

The first examination by one of us, on March 11, revealed typical closure of the central retinal artery of the right eye, with reduction of vision to light perception. In spite of the usual treatment with vasodilator drugs, vision was reduced to perception of hand motions temporally, superiorly and nasally. Examination six months later showed a sharp line of demarcation between the portion of the retina involved in the edematous process and that not involved, anterior to the equator of the eye (fig. 1).

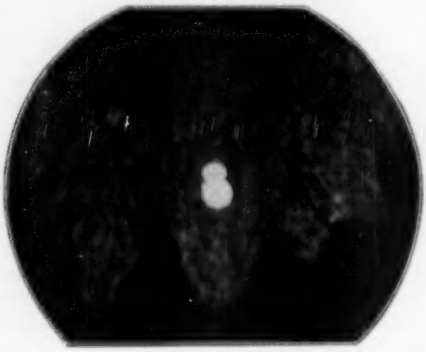
The coincidence was too striking to be dismissed as such. On observing another patient being given an anesthetic, it was seen that the tank and the tubes leading from the mask to the tank were always kept on the

right side, a condition which, because of the pulling of the tubes, would make the pressure on the right eye much greater than that on the left eye.

CASE 3.—Discussion of case 2 with a colleague uncovered the case of S. H., aged 37, bipara and trigravida, who was admitted to the hospital on Aug. 19, 1943. Delivery was by breech presentation; the membranes ruptured at the end of forty-five hours of labor. The cervix was fully dilated after eight and a half hours; the frank breech presentation did not advance, and extraction was decided on.

Pudendal block was induced, and general anesthesia with ether, nitrous oxide and oxygen was maintained via a closed system, using a facial mask. The baby was extracted alive. Fifteen minutes later the patient lost 500 cc. of blood and went into shock. Transfusions and infusions were given. Examination revealed a rupture of the cervix and lower uterine segment. Hysterectomy was decided on.

Atropine sulfate, 1/100 grain (6 mg.), was given by hypodermic injection. General anesthesia was maintained with ether, cyclopropane and oxygen, given via



Sharp line of demarcation between the involved and the uninvolved portion of the retina.

a closed system, using a rubber face mask. The anesthetic was given from the tank on the left side. The operation, on August 20, began at 2:15 a.m. and ended at 3:45 a.m. Suprapubic hysterectomy and right oophorectomy were performed. At 10 a.m. on August 20 the patient showed loss of vision in the left eye and ecchymosis of the lids of the left eye.

An ophthalmologic examination on August 21, by Dr. Ira Mensher, disclosed that the lids of the right eye were normal; there was edema of the upper and lower lids of the left eye, with chemosis of the bulbar conjunctiva; there was no proptosis. The right fundus was normal; the left disclosed typical closure of the central retinal artery. Dr. Algernon B. Reese, who saw the patient in consultation on the same day, found a "cherry red spot at the macula and hemorrhage between the disk and the macula. The impression was that of occlusion of the central retinal artery in the left eye."

Examination on September 1 showed the fundus to be stippled with small round pigment spots. All edema was absorbed. There was no visual recovery.

CASE 4 (reported by courtesy of Dr. William Grant).—A woman aged 40 was operated on for incisional hernia. Anesthesia was maintained with nitrous oxide, oxygen and ether, given in a closed mask, for two hours and forty-five minutes. The anesthetic was given from the tank on the right side. As soon as the patient came out of the anesthesia, she complained of loss of vision in the right eye. Examination showed closure of the central retinal artery, with a typical cherry red spot. The patient's nose had a shallow bridge. In spite of the usual treatment, no recovery of vision ensued.

Comment.—In cases 1, 2 and 4 the nasal bridges were low. The data on case 3 were not available. During the anesthesia, according to Rundle [1] exophthalmos of 2.25 mm. occurs. This, together with a low nasal bridge, would result in considerable pressure. With the mask in place and with exertion of slight pressure, the pressure on an eye of one of us was raised from 22 to 54 mm. of mercury, as measured with the Schiøtz tonometer, and this on a subject with a high nasal bridge.

In a rabbit under ether anesthesia, pressure applied to the sclera of a homatropinized eye for twenty minutes resulted in stoppage of all circulation. Edema of the retina and the cornea occurred, as well as segmentation of the blood column in both arteries and veins. On release of the pressure, hemorrhages appeared between the disk and the macula, and the edema disappeared completely in a few minutes. No permanent occlusion of the vessels could be made to occur.

A similar experiment carried out on a monkey (Macacus rhesus) did not produce permanent occlusion. Blood was drawn and the experiment repeated with the animal under pentobarbital sodium anesthesia (1 cc., or 1 grain [0.065 Gm.] per 5 pounds [2.3 Kg.] of body weight). The monkey weighed 8 pounds (3.6 Kg.) and was given 1.5 cc. intravenously. A canthotomy was done to allow for better pressure, which was exerted on the lateral aspect of the globe. No permanent occlusion resulted; only hyperemia of the optic disk was found. No shock, of course, was produced in either animal.

The question arises, what part does the loss of blood and shock play in the production of postanesthetic closure of the central retinal artery, and what part does pressure alone?

Retinal ischemia after exsanguination is a rare event, considering the common occurrence of profound loss of blood. It usually follows bleeding from medical conditions, and relatively rarely from wounds or surgical procedures. Recurrent hemorrhages are most prone to affect the vision. The resulting blindness is usually bilateral, but is unilateral in about 15 per cent of cases, and it may be transitory or permanent. It usually comes on between the third and the seventh day after bleeding,

1. Rundle, F. F.: West. J. Surg. **55**:578, 1947.

but may be delayed for some time. Terson's [2] statistics on its incidence follow:

Appearance of Blindness	Percentage Incidence
During the hemorrhage	8.3
Immediately after hemorrhage	11.6
Within 12 hours	14.2
Within 2 days	19.2
Between 3 and 16 days	39.2
Later than 16 days	7.5

Rarely, the picture is one of complete obstruction of the arterial circulation, occasionally even unilateral. Of this type is the case of Bonnet and Blanc, cited by Duke-Elder,[3] in which all light perception was lost. Two weeks later vision was 16.6 per cent and was limited to a small area around the fixation point.

A similar condition of ischemia may follow local causes in the orbit, such as trauma to the central retinal artery by accident. Pressure on the entering artery, according to Duke-Elder, may be like closure of the central retinal artery:

> The oedema is due to an avid imbibition of fluid caused by the osmotic attraction of catalytic products. The enzymes which in the normal alkaline retina take part in its metabolism, continue to break up metabolites to form acid products which cannot be dealt with, the increased osmotic activity of which leads to the imbibition of water and a swelling and loss of transparency of the tissues. The proteolytic enzymes then begin to act, hydrolyzing the intracellular proteins into smaller and smaller fragments and connecting the large molecular aggregates into simpler products which diffuse away, eventually leaving only the supporting tissue behind.[3]

Why does this condition not happen more frequently? At this time it seems that a combination of the following factors are needed: (1) loss of blood or shock; (2) pressure on the eye in a patient with a low nasal bridge and (3) prolonged anesthesia. It is quite possible that all or most of these factors in combination are needed for its development. Attention is called to the condition in that the main treatment consists perhaps in its prevention. The latter should be easy once attention of its possibility is called to the anesthetist and the surgeon.

Two observations in this study bear emphasis:

1. The appearance of hemorrhages in the rabbit on release of tension. Since this occurs in an apparently healthy animal, it should make one realize that hemorrhage occurring on release of tension in cases of glaucoma does not necessarily predicate diseased vessels.

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2. Terson, A.: Ann. d'ocul. 1922, p. 23.

3. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1940, p. 2557.

2. The sharp line of demarcation noted after healing in cases of closure of the central retinal artery. This has been described before but bears repetition.

Although the central retinal artery, as well as the posterior ciliary arteries, are cut, the degeneration of the retina is complete only at the posterior pole, and much less advanced toward the equator and anterior to it. Far anteriorly the entire retina, including the inner layers, is normal. Komoto has previously shown this. Since the only retinal blood supply available anteriorly is the anterior ciliary arteries, the whole anterior part of the retina can be nourished from the choroid —a fact which explains the limitation of the edema in obstruction of the central retinal artery to the posterior region. The degeneration and pigmentary disturbance noted months later coincide with the area of edema in the acute phase.

Since the collection and interpretation of the present cases, an article by Slocum and associates [4] has appeared on neurovascular complications due to malposition of the operating table. A case cited was that of a woman aged 55 who was operated on for section of the posterior fibers of the second division of the fifth nerve. A Bailey head rest was employed. During the procedure the head was pushed to one side and the forehead piece slipped, causing pressure on the right eye. Closure of the central retinal artery in the only remaining seeing eye ensued. A personal communication from Dr. Slocum included the following additional information:

Tribromoethanol solution–ether anesthesia was used for three hours; when the forehead brace slipped over the right eye, a sponge was placed over the eye to try to ease the pressure. This lasted for one hour and fifteen minutes. During the second hour the blood pressure was 80 systolic and 60 diastolic.

Dr. Slocum concluded:

> In view of one's knowledge of vascular complications in relation to pressure in other parts of the body, it can be reasoned that in this incident the external pressure against the globe may easily have contributed to the picture. The patient partially recovered vision in this eye in about three months.

CONCLUSIONS

This preliminary study is presented with the purpose of calling the attention of surgeons and anesthetists to what may not be a rare occurrence, namely, closure of the central retinal artery after general anesthesia, brought about in part by pressure on the globe of a patient who is in a state of shock with loss of blood. This complication might be prevented if the possibility is borne in mind.

108 East Sixty-Sixth Street (21).

4. Slocum, H. C.; O'Neal, K. C., and Allen, C. R.: Surg., Gynec. & Obst. **86**:729, 1948.

TRYPTOPHAN DETERMINATION IN CATARACTS DUE TO DEFICIENCY OR DELAYED SUPPLEMENTATION OF TRYPTOPHAN

A. J. SCHAEFFER, M.D.
AND
J. D. MURRAY
LOS ANGELES

IN SEVERAL recent papers it has clearly been shown that in dietary deficiencies not connected with ingestion of toxic substances, such as dinitrophenol, naphthalene, thallium and ergot, or with consumption of galactose, lactose or xylose, or with vitamin deficiencies, corneal vascularization, and often cataract formation as well, can be induced in experimental animals by inadequate diets in which the missing component is protein or one of its building stones, an essential amino acid. With protein deprivation (Hall and associates [1]) and with deficiencies of lysine and tryptophane (Totter and Day,[2]) of methionine (Berg and associates [3]), of phenylalanine, leucine and histidine (Maun, Cahill and Davis [4]) and of phenylalanine, isoleucine, threonine, valine and arginine (Sydenstricker, Hall, Bowles and co-workers[5]), corneal

1. Hall, W. K.; Sydenstricker, V. P.; Hock, C. W., and Bowles, L. L.: Protein Deprivation as a Cause of Vascularization of the Cornea in the Rat, J. Nutrition **32**:509, 1946.

2. Totter, J. R., and Day, P. L.: Cataract and Other Ocular Changes Resulting from Tryptophane Deficiency, J. Nutrition **24**:159, 1942.

3. Berg, J. L.; Pund, E. R.; Sydenstricker, V. P.; Hall, W. K.; Bowles, L. L., and Hock, C. W.: The Formation of Capillaries and Other Tissue Changes in the Cornea of the Methionine-Deficient Rat, J. Nutrition **33**:271, 1947.

4. Maun, M. E.; Cahill, W. M., and Davis, R. M.: Morphologic Studies of the Rats Deprived of Essential Amino Acids: I. Phenylalanine, Arch. Path. **39**: 294 (May) 1945; II. Leucine, ibid. **40**:137 (Sept.) 1945; III. Histidine, ibid. **41**: 25 (Jan.) 1946.

5. Bowles, L. L.: Vascularization of the Cornea of the Rat Resulting from Deficiencies of B Vitamins, Anat. Rec. **97**:381, 1947. Bowles, L. L.; Allen, L.; Sydenstricker, V. P.; Hock, C. W., and Hall, W. K.: The Development and Demonstration of Corneal Vascularization in Rats Deficient in Vitamin A and in Riboflavin, J. Nutrition **32**:19, 1946. Bowles, L. L.; Hall, W. K.; Sydenstricker, V. P., and Hock, C. W.: Corneal Changes in the Rat with Deficiencies of Pantothenic Acid and Pyridoxine, ibid. **37**:9, 1949. Hall, W. K., and Sydenstricker, V. P.: The Production of Methionine Deficiency in the Rat with Low Casein Diets, Arch. Biochem. **12**:147, 1947. Hall, W. K.; Sydenstricker, V. P.;

vascularization was commonly observed. Cataract formation was less common.

One of the earliest reports of cataract formation associated with dietary inadequacies in which protein or its components were involved is that of Curtis, Hauge and Kraybill,[6] who found that "rats receiving inadequate protein from either low corn protein or low protein of the basal ration in the absence of additions of trytophane developed permanent blindness. The blindness was characterized by white opaqueness of the eye and loss of the characteristic colors of the eye, quite different from ophthalmia due to vitamin A deficiency. All of the animals in lot . . . became totally blind about the sixth or seventh week." The authors concluded that "this condition appears to be due solely to tryptophane deficiency."

It seemed that this ocular lesion was due to lack of tryptophan, since addition of this essential amino acid to the diet prevented the formation of the lesion. The same form of cataract due to tryptophan deficiency was later reported by Totter and Day.[2] Buschke, Albanese and Follis[7] gave an exhaustive description of the morphologic characteristics of this type of cataract.

Cartwright and co-workers[8] maintained swine on synthetic diets in which protein was represented by an acid hydrolysate of casein or by zein. Obviously, these diets are primarily characterized by lack of tryptophan. All animals in these feeding experiments failed to grow, showed pronounced hypoproteinemia and died. Some of the animals exhibited cataract.

Hock, C. W., and Bowles, L. L.: Protein Deprivation as a Cause of Vascularization of the Cornea in the Rat, J. Nutrition **32**:509, 1946. Hall, W. K.; Bowles, L. L.; Sydenstricker, V. P., and Schmidt, H. L., Jr.: Cataracts Due to Deficiencies of Phenylalanine and of Histidine in the Rat: A Comparison with Other Types of Cataracts, ibid. **36**:277, 1948. Sydenstricker, V. P.; Hall, W. K.; Hock, C. W., and Pund, E. R.: Amino Acid and Protein Deficiencies as Causes of Corneal Vascularization: A Preliminary Report, Science **103**:194, 1946. Sydenstricker, V. P.; Hall, W. K.; Bowles, L. L., and Schmidt, H. L., Jr.: The Corneal Vascularization Resulting from Deficiencies of Amino Acids in the Rat, J. Nutrition **34**:481, 1947.

6. Curtis, P. B.; Hauge, S. M., and Kraybill, H. R.: The Nutritive Value of Certain Animal Protein Concentrates, J. Nutrition **5**:503, 1932.

7. (*a*) Buschke, W.: Classification of Experimental Cataracts in the Rat: Recent Observations on Cataract Associated with Tryptophane Deficiency and with Some Other Experimental Conditions, Arch. Ophth. **30**:735 (Dec.) 1943. (*b*) Buschke, W.; Albanese, A. A., and Follis, R. H.: Pathological Changes in Tryptophane Deficiency, Federation Proc. **1**:175, 1942.

8. Cartwright, G. E.; Wintrobe, M. M.; Buschke, W.; Follis, R. H., Jr.; Suiksta, A., and Humphreys, S.: Anemia, Hypoproteinemia and Cataracts in Swine Fed Casein Hydrolysate or Zein: Comparison with Pyridoxine-Deficiency Anemia, J. Clin. Investigation **24**:268, 1945.

In the last few years other investigators have succeeded in producing cataract by feeding diets deficient in various amino acids. Ferraro and Roizin [9] observed changes in the lens in animals fed a valine-deficient diet. In phenylalanine deficiency experiments, Sydenstricker and associates [8] noted, besides corneal vascularization, lenticular changes in 1 case. Repeating these experiments, these investigators noted in all but 2 of 25 rats definite lenticular changes, consisting of loss of transparency, which progressed until the death of the animal, at the twentieth to the thirtieth day. The same investigators reported having produced cataract by feeding a histidine-deficient diet. All the animals in this experiment which lived long enough exhibited lenticular opacities within ten to thirty-four days (mean, twenty-five days). They found also that superficial lenticular changes were reversed if the missing amino acid was added to the diet, the reversal of the changes depending on how far the changes had progressed. In the same series of experiments, the investigators produced cataract with tryptophan deficiency, confirming the results of earlier authors. In lenses from a series of animals used in investigation of other problems, similar changes were observed. These occurred in animals with deficiencies of threonine, leucine and isoleucine and in rats fed protein-free diets. In all the lenses the changes were similar to those described in phenylalanine deficiency, consisting of "haziness," visible separation of superficial fibers and widening of the sutures in varying degrees.

No less interesting is the report of Patch,[10] according to whom deprivation of cystine induced cataract formation in salamander larvae. An addition of 1.25 per cent cystine to the total protein intake prevented formation of this cataract. In these experiments the animals were fed a highly purified milk powder casein diet. Rezende and de Moura Campos [11] reported formation of cataract in rats fed a low protein diet. In their investigation, it seems, the diet represented a suboptimal supply of several amino acids. There were definite deficiencies of methionine and cystine.

Consideration of the increasing amount of experimental evidence on problems concerning ocular lesions due to disturbed protein metabo-

9. Ferraro, A., and Roizin, L. L.: Ocular Changes in Rats on Amino Acid (Tryptophane) Deficiency Diets, Am. J. Ophth. **29**:1013, 1946; Ocular Changes in Rats on Amino Acid (Valine) Deficiency Diet, ibid. **30**:330, 1947.

10. Patch, E. M.: Cataracts as a Result of Dietary Deficiency in Larval Amblyostoma Tigrinum, Science **79**:57, 1934; Cataracts in Amblyostoma Tigrinum Larvae Fed Experimental Diets, Proc. Soc. Exper. Biol. & Med. **46**:205, 1941; Dietary Production of Cataracts in Larvae Amblyostoma Tigrinum, J. Nutrition **22**:365, 1941; Relation of Diet to Lenticular Changes in Larvae of Amblyostoma Tigrinum, Arch. Ophth. **29**:69 (Jan.) 1943.

11. Rezende, C., and de Moura Campos, F. A.: Cataracts in Rats Fed a Low Protein Diet, Arch. Ophth. **28**:1038 (Dec.) 1942.

lism leads to an important observation. While any experimental modality of the dietary disturbance results in corneal vascularization, as well as in arrest of growth in the young animal, cataract formation is rarely observed. Logically, the development of cataract in these experiments may be the result of disturbed protein synthesis due to the absence of one or more essential amino acids; or it may be that certain amino acids, deficiencies of which induce cataract, have a specific role in the metabolism of the lens. On the other hand, the other amino acids are devoid of such a role. Their presence or absence will not affect fundamentally the physiologic processes of the lens, and their absence will not result in cataract.

Our intention in the present study is to investigate this problem by the method of delayed supplementation of tryptophan. This method of attack, established by Geiger,[12] has furnished many valuable data concerning problems of metabolism. It has shown that infant rats, given a diet of incomplete amino acid mixtures, did not grow if the missing amino acid was fed separately from the rest of the diet several hours later. These experiments indicated that amino acids are not stored in the body and that protein synthesis can proceed only when all essential amino acids are present simultaneously in the tissues. If the delayed supplementation of tryptophan should prevent cataract formation without promoting growth, we might conclude that this amino acid exerts a protective action independent of protein synthesis. Such a possibility was suggested by Cahill and Kotalik,[13] who found that abrine (1-methyl-tryptophan), which is not sufficient in promoting growth, prevented cataract in animals fed tryptophan-free diets. Should delayed supplementation of tryptophan, on the other hand, fail to prevent cataract formation, there is support for the hypothesis that cataract formation is solely the result of inability of the body to synthesize protein from an inadequate mixture of amino acids; i.e., basically it is a protein depletion cataract.

METHODS OF DELAYED SUPPLEMENTATION OF TRYPTOPHAN

Method.—The first series of experiments (carried out together with Dr. E. Geiger) were performed on pure bred Sprague-Dawley rats, placed in cages with wire mesh bottoms. Special food containers were employed to prevent the food being spilled (Geiger [12]). Infant rats with body weights of 35 to 45 Gm. were used in two groups of 6 each. The first group was fed tryptophan-deficient diet 1 for twelve hours and diet 2, containing tryptophan, for the next twelve

12. Geiger, E.: Physiology of the Utilization of Dietary Amino Acid Mixtures, Dissertation, University of Southern California, Los Angeles, 1947; Experiments with Delayed Supplementation of Incomplete Amino Acid Mixtures, J. Nutrition **34**:97, 1947.

13. Cahill, W. M., and Kotalik, G. C.: Some Observations on Abrine, J. Nutrition **26**:471, 1943.

hours. The second group received, similarly, diet 1 for twelve hours and diet 2 for twelve hours, but between the two diets all food was withdrawn for the duration of one hour, when diets were changed in this group.

The composition of the diets was as follows:

Diet 1: Acid-hydrolyzed fish protein, 30 Gm., and basal diet, 70 Gm.

Diet 2: L-(—) tryptophan, 6 Gm., and basal diet, 94 Gm.

Basal diet:

	Gm.	Per Cent of Total Body Weight
U. S. P. XII salt mixture II	200	5.13
Rice bran concentrate	400	10.26
Cottonseed oil U. S. P.	200	5.13
Fish oil	50	1.27
Vitamin A	1 Gm. (3,000 I. U.)	
Vitamin D	1 Gm. (400 I. U.)	
Starch U. S. P.	2,450	78.20
Riboflavin	75 mg.	
Calcium pantothenate	150 mg.	
Choline chloride	2.5 mg.	

The amino acid solutions were prepared by Dr. Geiger from fish protein. This protein was isolated from edible mackerel by isoelectric precipitation and consecutive solvent extraction. The biologic evaluation of this protein has been reported (Deuel and associates [14]) and found to be higher than that of casein. The protein was hydrolyzed with sulfuric acid at 15 pounds (6.8 Kg.) pressure for eight hours. The sulfuric acid was removed and the material concentrated

TABLE 1.—*Composition of the Spray-Dried Fish Protein Hydrolysate* *

	Per Cent
Total nitrogen (Kjeldahl method)	13.45
Ash	2.32
Moisture	6.7
Amino acids (values calculated to 16% nitrogen	
Arginine	6.36
Glutamic acid	14.2
Aminoacetic acid	7.44
Histidine	3.18
Isoleucine	7.70
Leucine	11.8
Lysine	11.4
Methionine	4.0
Phenylalanine	4.74
Threonine	5.23
Tyrosine	1.55
Valine	7.44
Cystine	2.1
Addition of tryptophan was 1.39 per cent for control animals	

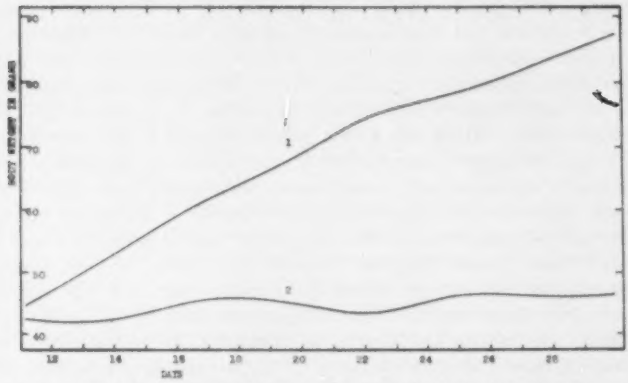
* The amino acids were determined by the chemical methods described by Block, R. J., and Bolling, D.: Amino Acid Composition of Proteins and Foods, Springfield, Ill., Charles C Thomas, Publisher, 1945, and by the microbiologic methods developed and used in the laboratory of Prof. Max Dunn.

and the spray dried. The tryptophan in these hydrolysates is completely destroyed, and thus it represents the incomplete amino acid mixture necessary for the present experiments, as is evidenced by its amino acid analysis (table 1).

14. Deuel, H. J.; Hrubetz, M. C.; Johnston, C. H.; Winzler, R. J.; Geiger, E., and Schnakenberg, G.: Studies in the Nutritive Value of Fish Proteins: I. Evaluation by the Rat Growth Method and by the Cannon Method, J. Nutrition **31**:175, 1946.

Results.—Animals given delayed tryptophan supplementation showed a growth curve similar to that of animals fed diets lacking tryptophan entirely. Since the experiments of Berg and associates,[9] it has been known that young rats with tryptophan deficiency cease to grow, a phenomenon characteristic of, but not specific to, tryptophan deficiency, as it is commonly observed in deficiencies of other essential amino acids and in protein depletion.

Curve 2 in the chart shows clearly a similar arrest of growth of rats fed with delayed tryptophan supplementation. This curve is nearly identical with the growth curve of the animals of the second series of experiments, in which a pure form of tryptophan deficiency cataract was produced by feeding the described fish protein hydrolysate without



Body weight of rats in experiment with delayed supplementation of L-(—)-tryptophan.[12] Curve *1* represents values for animals receiving a diet complete in essential amino acids; curve *2*, values for animals fed alternately incomplete mixture and tryptophan at twelve hour intervals.

the addition of tryptophan. The control animals were given the same diet except that 1 per cent of L (—) tryptophan was added. These animals showed an average increase in body weight of 4 to 5 Gm. daily, their growth curve (curve *1*) being similar to that of animals fed on regular non-synthetic diets.

In spite of an adequate supply of tryptophan derived from the two diets consumed within twenty-four hours, the experimental rats failed to show normal growth. This again demonstrates that tryptophan fed apart from other amino acids cannot be utilized for protein synthesis. We did not observe the alopecia or hyperexcitability described by Totter and Day,[2] as well as by Buschke, Albanese and Follis.[7b] These

symptoms probably resulted from other nutritional deficiencies (perhaps of certain vitamins).

The ocular changes were as follows: Lenticular involvement with corneal vascularization was noted in 10 of the 12 experimental animals, although in all the animals corneal vascularization of some degree occurred. This vascularization was the first manifestation in the animals with delayed tryptophan supplementation. In the control animals, receiving protein hydrolysate with added tryptophan, the symptom of vascularization was entirely missing. On the other hand, in all animals of the second experiment, fed a diet totally free from tryptophan, the vascularization was observed.

In the development of vascularization in animals fed with delayed supplementation of tryptophan and in the rats fed a diet completely lacking in tryptophan there was a slight, but definite, difference in time before the first sign appeared. While in animals on tryptophan-deficient diets the corneal lesion was noticed at the thirteenth day of the experiment, in animals receiving delayed tryptophan supplementation the first sign appeared only toward the middle of the third week. The corneal vessels, originating in the pericorneal plexus, ran superficially as straight or slightly tortuous loops, mostly in radial direction toward the center of the cornea. Anastomoses between the loops were commonly encountered. Blood was noted, especially in the larger vessels. The corneal vascularization has repeatedly been described by Bessey and Wolbach[15] and Buschke, Albanese and Follis.[7b] Our findings both in rats fed tryptophan-free diets and in rats fed with delayed tryptophan supplementation were identical with those in rats fed by these authors. A "steamy," or cloudy, appearance of the entire cornea was noticed in only 2 of the animals fed the tryptophan-free diet and in 4 of the rats fed with delayed tryptophan supplementation. The lenticular alterations, also, called to mind descriptions of previous authors, although these changes showed a certain variability, especially in the earlier stages and in the configuration of the opacities.

Lenticular involvement, together with corneal vascularization, was noted in 10 of the 12 experimental animals. The 2 animals with no sign of cataract had been on the experimental diet for only six weeks. The opacities were first noted subcapsularly but gradually involved most of the posterior cortex and in 2 cases progressed to the anterior cortex, the nucleus and, finally, the entire lens.

The shape of the opacities showed considerable variation. In 1 animal the opacification involved the central portion of the posterior cortex, forming a flower-shaped figure, while the peripheral region

15. Bessey, O. A., and Wolbach, S. B.: Vascularization of the Cornea of the Rat in Riboflavin Deficiency with a Note on Corneal Vascularization in Vitamin A Deficiency, J. Exper. Med. **69**:1, 1939.

remained clear. In other rats the peripheral margin showed denser opacities, while the central area remained clear. The suture lines became visible; dehiscence of the lines, clefts filled with fluid and vacuoles became increasingly noticeable. In a few cases the anterior cortex became involved, principally in the equatorial region. In 2 cases this development was followed by progressive intensification of the milky, diffusely opaque appearance of the whole lens.

The period of development also showed striking variations. In most cases some definite sign of cataract formation could be observed by the sixth week of the experiment. In the 2 cases in which development of cataract proceeded furthest, incipient signs had been noted by the fourth week of the experiment, with a rapid subsequent course. By the twelfth week the lenses in these animals appeared whitish and opaque to the unaided eye, whereas in other animals only posterior cortical opacities were observed.

These results are similar to, if not identical with, the growth and ocular manifestations noted in the studies on rats fed tryptophan-deficient diets. There were no clinical differences with respect to corneal vascularization and cataract formation between animals completely deprived of tryptophan and those receiving delayed supplementation of the amino acid.

In these experiments, ocular symptoms developed in spite of the fact that the rats ingested relatively large quantities of tryptophan (0.1 to 0.2 Gm. a day). Prevention of cataract, like promotion of growth, can be achieved only if tryptophan is supplied simultaneously with the other essential amino acids. This suggests a possible causal relation of disturbed protein synthesis to cataract formation. Further investigation is required as to why disturbance of protein synthesis from the lack of essential amino acids other than tryptophan and histidine does not result in cataract formation.

TRYPTOPHAN CONTENT OF THE LENS WITH TRYPTOPHAN DEFICIENCY CATARACT

The results of the foregoing investigations indicate that tryptophan is not "specifically" indispensable. The tryptophan deficiency cataract is actually a protein depletion cataract. If tryptophan is missing from the diet, or is supplied to the animal at a time when the other amino acids are absent, protein synthesis cannot be accomplished, and cataract is one of the results.

The validity of this hypothesis can be investigated further by determination of the tryptophan content of the normal and of the cataractous lens. This was done in the following experiments.

The experiments were performed on infant rats (35 to 45 Gm. of body weight) in two groups consisting of 7 and 6 rats, respectively. The third

(control) group consisted of 8 rats. The diet of the experimental animals, the first two groups, consisted of 30 Gm. of acid-hydrolyzed fish protein and 70 Gm. of basal diet (the same as diet 1 of the foregoing experiments with delayed tryptophan supplementation).

The results regarding growth were essentially the same as those reported in previous studies by Geiger [15] and Schaeffer and Geiger.[16] In the first two groups of experimental animals, lenticular and corneal changes developed. These changes have repeatedly been described elsewhere. Corneal vascularization of different degrees was noted in all experimental animals. In the first group 3 cataracts, and in the second group only 1 cataract, developed to an advanced stage, although in most of the animals the incipient stage of cataract formation was apparent at the time they were killed and their lenses, in capsule, used for microbiologic determination of tryptophan.

Method.—All lenses of each group were examined together, but those for each group were studied separately.

Moisture was determined on the total sample by drying in a vacuum at 40 C. The ash content was determined on a portion of the dried sample in each case.

TABLE 2.—*Tryptophan Content of Normal Lenses and Tryptophan Deficiency Cataract Lens in Rats*

	Percentage of Moisture in Fresh Lens Substance*	Determinations on Dry Weight, %				Percentage of Tryptophan in Dry Protein
		Ash	Nitrogen	Protein	Tryptophan	
Tryptophan deficiency cataract lens group 1	69.9	1.77	16.7	95.3	2.06	2.1
Tryptophan deficiency cataract lens group 2	69.0	1.98	16.3	93.4	2.08	2.18
Lenses of control animals	61.5	1.66	18.9	100	2.80	2.9

* Some of the moisture may have been lost in handling the material (freezing and defreezing).

The samples were hydrolyzed by being autoclaved twenty-four hours in sealed tubes with a five times normal sodium hydroxide solution. Nitrogen was determined on an aliquot of the hydrolysate, and the remaining hydrolysate was assayed for tryptophan by the well known microbiologic assay method, using Lactobacillus arabinosus. With the microbiologic assay method, Schaeffer and Shankman [17] and Schaeffer and Murray [18] attempted to complete the amino acid determination of the various tissue proteins of the eye.

Results of the analyses are given in table 2.

Conclusion.—There was no significant difference in the tryptophan content of the lens protein in the eyes of normally fed rats and that of rats fed a tryptophan-free diet. This result serves to support the conclusion drawn from the results of earlier work. In diets deficient

16. Schaeffer, A. J., and Geiger, E.: Cataract Development in Animals with Delayed Supplementation of Tryptophane, Proc. Soc. Exper. Biol. & Med. **66**:309, 1947.

17. Schaeffer, A. J., and Shankman, S.: Amino Acid Composition of the Ocular Tissues, Am. J. Ophth., to be published.

18. Schaeffer, A. J., and Murray, J. D.: Amino Acid Composition of the Bovine Lens, to be published.

in essential amino acids, the protein synthesis principally seems to be disturbed. The animal body is not able to form protein from a mixture of amino acids which is lacking in one of the necessary components, e.g., tryptophan. Thus, in the lens proteins of tryptophan deficiency cataract the tryptophan is expected to be found in the same proportion as in the proteins of the normal lens.

COMMENT

The results of these experiments confirm previous observations of Geiger [12] showing decisively that delayed supplementation of tryptophan is not effective. It does not promote growth or prevent development of ocular lesions, i.e., corneal vascularization and cataract formation. This amino acid can be utilized for protein synthesis only when it is fed simultaneously with the other essential amino acids. An essential amino acid, in this case tryptophan, cannot be stored in the body but is readily metabolized.

Experiments with delayed supplementation with lysine and methionine, as well as with tryptophan, showed the same arrest of growth, indicating that all the essential amino acids must be simultaneously present in the diet for protein synthesis to be accomplished. The corneal vascularization and cataract formation are probably only partial phenomena of the essential amino acid deficiency. Both the arrest of growth and the ocular lesions are undoubtedly due to deprivation of protein. The body is unable to synthesize protein when any one of the building stones of the protein molecule is absent, and the missing component cannot be utilized even a short time after ingestion of the others. Thus, the cataract is not specifically a "tryptophan deficiency cataract" but is, essentially, a cataract due to protein depletion (Schaeffer and Geiger [16]).

If this contention can be further substantiated, the lack or delayed supplementation of any of the other essential amino acids, or protein deprivation, can be expected to induce the same, or at least a similar, ocular lesion. Since the preliminary report of Schaeffer and Geiger,[16] in which it was suggested that experimentation with any of the essential amino acids should give similar results, the number of reports of cataracts due to amino acid deficiencies has increased considerably. All investigators have described the same arrest of growth of the young animals fed diets lacking in one of the essential amino acids. At the same time, in all these experiments the same corneal lesion, vascularization, is observed. Logically, cataract formation should follow uniformly with the other two deficiency symptoms in parallel experiments. All have the same common denominator, namely, the inability of the lens to synthesize protein, and therefore protein deprivation.

The growing list of cataracts due to amino acid deficiencies, i.e., deficiencies of tryptophan, valine, phenylalanine, histidine, threonine, leucine, isoleucine and methionine, makes it seem very likely that the lenticular changes represent a partial or parallel phenomenon with the arrest of growth and the corneal vascularization, and that these changes will be manifest in any nutritional work characterized by lack of any of the essential amino acids.

This theory considers only one of the main functions of the amino acids, that of being a building stone for protein synthesis. While specific roles are known, even the important role, that of protein metabolism, with which this work is concerned, is poorly understood. The mechanics of utilization and the specific functions of the individual amino acids and their role in the formation of various proteins do not seem to be uniform. The different amino acids have different significance in the body.

Osborne and Mendel (1915)[19] showed that tryptophan is essential for both growth and maintenance, while lysine is essential only for growth. Rose and Rice[20] showed differences of arginine requirements in growing and in adult animals.

The amino acids introduced into the body may normally undergo any of several changes, such as various types of deamination and/or oxidation yielding hydroxy acids, keto aldehydes, hydroxyamino acids, keto acids and fatty acids, the nitrogenous products generally going to form urea, which is eliminated by the kidneys, and the other products being further degraded or used as intermediate substances in synthesis of other compounds, such as fats and carbohydrates.

The individual roles of the amino acids are in great part completely unknown, although many of their functions have been thoroughly investigated, i.e., the role of methionine or cystine in the formation of taurine and taurocholic acid and their detoxifying action; the role of tyrosine in the formation of melanine, epinephrine and the thyroid hormone; the role of histidine in the formation of purine and histamine, and the role of aminoacetic acid in the formation of glycocholic and guanidoacetic acids.

Concerning the mechanism of protein synthesis from amino acids, however, present knowledge does not go much beyond the basic experiments of Löwy and Abderhalden and a few contemporary investigators.

Important to the present point of view is the principle which is made apparent by the results of the present investigation, namely, that

19. Osborne, T. B., and Mendel, L. B.: The Comparative Nutritive Value of Certain Proteins in Growth, J. Biol. Chem. **20**:351, 1915.

20. Rose, W. C.: The Role of the Amino Acids in Human Nutrition, Proc. Am. Phil. Soc. **91**:1, 1947. Rose, W. C., and Rice, E. E.: Significance of the Amino Acids in Canine Nutrition, Science **90**:186, 1939.

all the so-called essential amino acids are equally required for normal protein metabolism of the lens, and that deficiency of any one results in formation of cataract.

This "principle" gains credence if one considers the list of the amino acids considered essential: lysine, tryptophan, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine. Of these, arginine is not in the strictest sense essential. The rat organism is able to synthesize it, although not in sufficient quantity to satisfy all growth requirements, and thus it might be listed among the essentials. Furthermore, its essentiality in various animal species, e.g., in human beings, has not yet been determined.

Since cataract formation has been demonstrated to result from deficiencies of all but two of the essential amino acids (exclusive of arginine), one may logically expect that future research will show that all these amino acids are essential to the normal metabolism of the lens. Of course, it is known that the quantitative, and in some respects the qualitative, requirements for individual amino acids vary with species and with age, and probably also with sex, according to their specific utilization for physiologic purposes. By "requirement" is meant satisfaction of the total need for the specific functions and for synthesis of new protein in growth and maintenance. Human requirements for individual amino acids have been studied in the last few years. Rose and associates demonstrated clearly (experimenting on graduate students) that the nitrogen balance in the body cannot be maintained with dietary deficiencies of valine, methionine, threonine, leucine, isoleucine, phenylalanine, alanine, tryptophan or lysine. A surprising finding in these investigations was that histidine, an amino acid essential for all animal species studied, was found dispensable for the human adult. In spite of its exclusion from the diet, no change in nitrogen balance could be detected. A similar result was obtained with arginine. The absence of these two amino acids from the diet produced no loss in body weight or changes in the nitrogen balance. The conclusion is that histidine and arginine are not essential for maintenance in the human adult. The requirements of these two amino acids for human growth have not been determined.

In all these studies the qualitative requirements were established, and the quantitative requirements, i.e., the minimal level compatible with maintenance of nitrogen balance, could also be approximated. In this way the limits of the daily requirements of the individual indispensable amino acids were established. The acquired knowledge may provide dietary minima and optima. While minima and optima and safety margins are important, the time factor should be considered as carefully as other dietary factors in view of the results of the present work with delayed supplementation.

The consequences of these considerations are obvious. Within the category of cataracts due to nutritional inadequacies, those due to protein or amino acid deficiencies are gaining in interest. How far such deficiencies play a role, if only partial, in human senile cataract is not understood, but it would not be surprising if such a correlation could be demonstrated. Characteristically, in earlier investigations of the problem of cataract certain correlations between senile cataract and senile changes of the endocrine system were sought (Siegrist [21]), an attempt theoretically justified. Since the experimental production of nutritional cataracts became a routine tool of laboratory investigation, a problem that is becoming more and more pressing is whether nutritional irrationalities among persons in the higher age groups are generally not underestimated. On the basis of our observations, one can logically advance the following questions:

1. Is the nutrition of the aged not often qualitatively and quantitatively inadequate owing to certain faulty considerations of the age, just as decades ago faulty alimentation was common in the infant, leading to considerable number of cases of avitaminoses, besides other forms of malnutrition (Schaeffer [22])?

2. May not the time factor in this hypothetic malnutrition of the aged be such as to contribute in the long run to the development of the senile cataract?

3. May not faulty considerations of the aged lead to pathologic changes in other parts of the body, which may parallel the ocular changes? In this category may be enumerated senile changes, of which gerontology furnishes many examples.

Unexplained as yet, of course, is the great similarity of the tryptophan deficiency cataract to the cataract of riboflavin deficiency, but there is the probability that both changes are due to partial inanition.

Results of the present investigations bear on another important ophthalmologic problem, namely, the metabolism of the lens. Our findings suggest that the nitrogen metabolism of the lens is considerable, probably like that of some other parts of the body.

All previous biochemical investigations have indicated that the lens has a purely carbohydrate metabolism, as its respiratory quotient is equal to 1. The early investigations of Fischer led to the hypothesis that carbohydrates represent the only substance necessary for supplying the metabolic needs of the lens. This hypothesis was supported by

21. Siegrist, A.: Der graue Altersstar, Vienna, Urban & Schwarzenberg, 1928.

22. Schaeffer, A. J.: Le vitamine nei loro rapporti con l'oftalmologia, Documenta Ophthalmologica **1**:271, 1938; Some Aspects of Ophthalmo-Pharmacology: I. Fundamental Principles, ibid., vol. 4, to be published.

quantitative measurements of the glucose content of the normal and the cataractous lens (O'Brien and Salit,[23] Weekers [24]) and the glycolytic ability of the lens (Campos,[25] Ferrara,[26] Michail and Vancea,[27] Kronfeld and Bothman [28]), showing that the lens utilizes a considerable amount of glucose, converting it into lactic acid. As for the glycolysis, the lens carries on a complex oxidation-reduction process, in which ascorbic acid and glutathione seem to play important roles. Krause expressed his doubt whether the study of carbohydrate metabolism would exhaust the entire problem of lenticular metabolism. Glutathione is not necessarily concerned with carbohydrate oxidation; it may, rather, be involved in the process of protein synthesis.

We have seen that in protein depletion or in deficiency of one of the essential amino acids the whole organism suffers: The young organism is unable to grow; the adult organism loses weight. Among the early symptoms are vascularization of the cornea and cataract formation. Such deficiency phenomena clearly indicate that there is a metabolic exchange of the deficiency factor, independent of the modalities of the requirement or of its biologic purpose. The physiologic function of this nutritional factor in the metabolism of the lens is clearly suggested in these experiments. Such problems, though they are not directly involved in the present experiments, invite further investigation.

SUMMARY

1. Experiments with delayed supplementation of tryptophan show that cataract formation in rats occurs even after consumption of relatively large quantities of tryptophan. It seems that, like growth promotion, prevention of cataract by this amino acid can be accomplished only when it is supplied simultaneously with the other essential amino acids.

2. There is no considerable difference between the tryptophan content of the lens protein in eyes of normally fed rats and that of rats on a diet lacking tryptophan. This finding coincides with the

23. O'Brien, C. S., and Salit, P. W.: Chemical Constituents of Aqueous, Vitreous, and Lens: Comparative Study on Animal Eyes, Am. J. Ophth. **14**:582. 1931.

24. Weekers, R.: L'acide lactique du cristallin, Arch. d'opht. **1**:707, 1937.

25. Campos, R.: Ricerche sulla respirazione e sulla glicolisi del cristallino, Riv. di pat. sper. **8**:217, 1937.

26. Ferrara, A.: Glicolisi e respirazione del cristallino nella cataratta naftalinica, Ann. di ottal. e clin. ocul. **66**:862, 1938; Respirazione e glicolisi del cristallino di cavie sottoposte a dieta scorbutigena, ibid. **68**:529, 1940.

27. Michail, D., and Vancea, P.: Nouvelles recherches sur le pouvoir glycolytique du critallin, Compt. rend. Soc. de biol. **109**:317, 1932.

28. Kronfeld, P., and Bothman, L.: Zur Frage der Linsenatmung, Ztschr. f. Augenh. **65**:41, 1928.

conclusions from our earlier experiments,[29] namely, that in diets deficient in essential amino acids, the protein synthesis is principally disturbed. Either the animal body can synthesize the protein characteristic for its body, or it cannot synthesize protein at all. It is not able to form a protein molecule from available inadequate building stones, in this case proteins deficient in tryptophan. Thus, in the proteins of lenses with tryptophan deficiency cataracts the tryptophan is in the same proportion as in the proteins of the normal lens. The inability to synthesize protein is evidenced by lack of growth.

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29. Schaeffer and Geiger.[16] Schaeffer and Shankman.[17] Schaeffer and Murray.[18]

OPHTHALMOPLEGIA AND PIGMENTARY DEGENERATION OF THE RETINA

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THE ASSOCIATION of retinal degeneration and neurologic disorders is well known. Prominent among these is cerebromacular degeneration, or amaurotic familial idiocy. The association of pigmentary degeneration of the retina with neurologic disorders is best known in the Laurence-Moon-Biedl syndrome, which includes mental retardation. Still other heredodegenerative diseases of the nervous system reported to be associated with pigmentary degeneration of the retina are Friedreich's ataxia,[1] progressive dementia,[2] the cerebellopyramidal syndrome [3] and spastic [4] and flaccid [5] paraplegias.

In 1944, Barnard and Scholz [6] reported 4 cases of ophthalmoplegia with pigmentary degeneration of the retina and concluded that they all represented a single syndrome with a common etiologic factor.

Walsh [7] concurred in this opinion and described 4 cases of a similar disorder. His case 224 appears to be the same as case 4 of Barnard and Scholz; thus a total of 7 such cases have been reported.

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From the Ophthalmologic Service of Dr. Samuel Gartner, Montefiore Hospital for Chronic Disease.

1. Zonca, G.: Eredo atassia cerebellospinale and alterazione retiniche, Atti Cong. Soc. oftal. ital., 1938, pp. 721-728.

2. von Stock, W.: Ueber eine bis jetzt noch nicht beschriebene Form der familiär auftretenden Netzhautdegeneration bei gleichzeitiger Verblödung, und über typische Pigmentdegeneration der Netzhaut, Klin. Monatsbl. f. Augenh. **46**:225-244, 1908.

3. Froment, J.; Bonnet, P., and Colrat, A.: Hérédo-dégénération rétinienne et spinocérébélleuse, J. de méd. de Lyon **18**:153-162, 1937.

4. Clauss, O.: Ueber hereditäre cerebellare Ataxie in Verbindung mit Pigmentdegeneration der Retina und Degeneration des N. cochlearis, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:294-298, 1924.

5. Ruggeri, R.: Su una complessa sindrome famiglare: L'eredodegenerazione acustico-ottico-cerebro-spinale, Pediat. rev. **48**:117-124, 1940.

6. Barnard, R. I., and Scholz, R. O.: Ophthalmoplegia and Retinal Degeneration, Am. J. Ophth. **27**:621-624, 1944.

7. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 769.

In 5 of these 7 cases the onset was known to have occurred during the second decade of life, and in the other 2 cases, at the ages of 30 and 33. In only 2 of the cases was a family history of similar difficulties obtainable. In 5 of the cases there was a complaint of failing vision at one time or another. Studies of the visual field were reported in 6 of the 7 cases, and only in 1 case was a defect found—case 3 of Barnard and Scholz, in which the macular areas were involved by the pigmentary degeneration and corresponding central scotomas were found. The peripheral fields were reported as normal in all the 6 cases. In all 7 cases there was generalized limitation of ocular motility, as well as ptosis in 4 cases. In no case was internal ophthalmoplegia present. In all 7 cases some pigmentary degenerative changes were evident in the retina; these lesions varied from a pigmentary mottling, in most of the cases, to true bone corpuscle formation, in 2 of them. In only 2 cases did the other fundic features of true primary pigmentary degeneration of the retina exist, that is, narrowing of the vessels and pallor of the disks. In summary, the features common to all these cases were an insidious onset of chronic, progressive external ophthalmoplegia and the development of atypical pigmentary degeneration of the retina in adolescence or early adult life.

Fig. 1 (case 1).—*A*, direct view; *B*, patient in attempt to raise the lids; *C*, patient in attempt at right lateral gaze; *D*, patient in attempt at left lateral gaze.

We report 3 cases which we believe represent this syndrome.

REPORT OF CASES

Case 1.—M. K., a 13 year old boy, was said to be "neurotic and spoiled." At 11 years of age he began to have difficulty in opening his eyes. None of the other members of his family had a similar complaint. Except for the ocular condition, short stature and lack of gonadal development for a boy of his age, the physical examination showed nothing remarkable.

Ocular Examination.—Vision without correction was 15/70 in the right eye and 15/100 in the left eye. With a correction of —2.50 cyl., axis 180, vision was 15/30 in each eye. The pupils were round and equal and reacted well to light.

Ptosis was almost complete in both eyes, so that the patient had to tilt his head back in order to see well enough to get around. Ocular motility was restricted in all directions. On attempted right lateral gaze, the right eye could rotate 45 degrees and the left eye 30 degrees. On attempted left lateral gaze, the right eye rotated only 15 degrees and the left eye 30 degrees. Upward gaze was present but limited. Both fundi showed irregularly distributed pigment granules in the macular area, as well as throughout most of the periphery. Some of this pigment lay anterior to the retinal vessels. The disks were of normal color and the vessels of normal caliber. The peripheral visual fields for 2/330 white showed slight peripheral contraction. Studies of the central fields were not satisfactory.

The rest of the investigation, consisting of a test for myasthenia gravis with neostigmine, audiometric and caloric tests and roentgenographic studies of the skull, together with routine examinations of the blood and urine and serologic tests, was noncontributory.

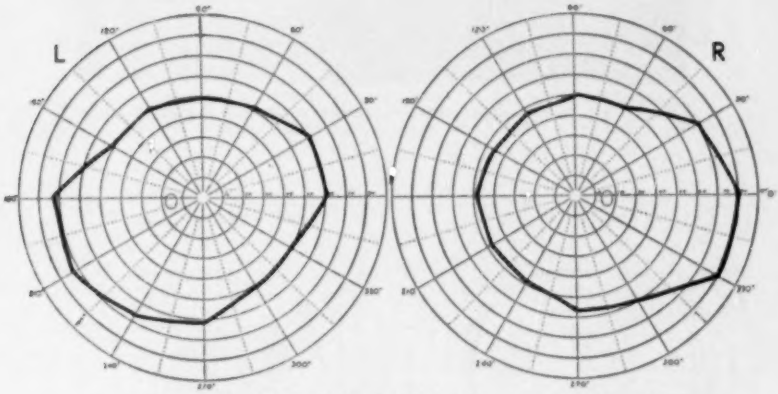

Fig. 2 (case 1).—Peripheral fields for 2/330 white show a questionable degree of irregular peripheral indentation in the left upper temporal field.

Case 2.—T. I., a 14 year old white girl, on Aug. 5, 1948 suddenly lost vision in the right eye. Her past history revealed an insidious, progressive onset of ptosis two years before, at the age of 12, so that, on admission, she had to wrinkle her forehead in order to raise the lids high enough to enable her to see how to get around. The family history was not contributory. In addition to the ocular condition, physical examination revealed only impairment of bone conduction in hearing and a rather small stature for a child of her age.

Ocular Examination.—Vision with correction was reduced to perception of hand movements in the right eye and was 15/20 + in the left eye. The right pupil measured 4 mm., and the left pupil 2 mm., in diameter. Light thrown into the right eye produced no pupillary response, but light thrown into the left eye caused contraction of both pupils.

Ocular motility was restricted. On attempted left lateral gaze, the right eye was able to adduct 25 degrees and the left eye abducted 30 degrees. On attempted right lateral gaze, both eyes rotated only 25 degrees from the midline.

The media were clear, and the fundi were easily visualized. Examination of the right fundus showed definite swelling of the disk with blurred margins and distended veins. Several small linear hemorrhages were seen coming off the disk, and the retinal arteries were slightly narrowed. The disk and vessels of the left eye were normal in appearance and showed none of the features of papillitis seen in the disk of the right eye. Throughout both fundi, especially peripherally, there

Fig. 3 (case 2).—*A*, direct view; *B*, patient in attempt at upward gaze; *C*, patient in attempt at right lateral gaze; *D*, patient in attempt at left lateral gaze.

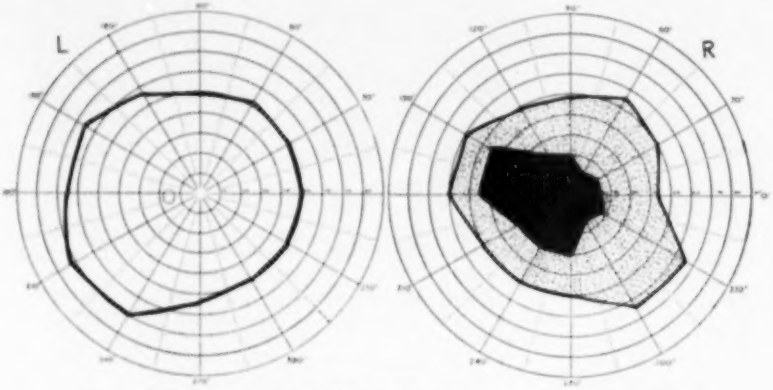

Fig. 4 (case 2).—The right field for 5/330 white shows a dense central scotoma and some peripheral depression compatible with the acute papillitis. The left eye shows a normal peripheral field for 1/330 white.

were irregular areas of pigmentary retinal degeneration, manifested by yellowish mottling with fine and coarse pigment deposits. No definite formation of bone corpuscles was made out; rather, the picture resembled a fundus of the "salt and pepper" type.

Studies of the visual field were carried out four days after the patient's admission, at which time she began to describe some improvement in vision in the right eye with optic neuritis. The left eye showed normal peripheral fields for

1/330 white. Studies of the right eye with 5/330 white showed a large, dense central scotoma, as well as a general, over-all depression of the entire field of vision.

Spinal puncture revealed that the pressure, dynamics and chemical constituents of the fluid were normal. The results of urinalysis, blood chemical determinations, blood count and serologic tests were normal. Roentgenograms of the skull and electroencephalograms also showed no abnormality.

Case 3.—K. B., a white woman aged 26, was admitted to the hospital in October 1947, with the history that at the age of 13 both upper eyelids had begun

Fig. 5 (case 3).—*A*, direct view; *B*, patient in attempt to raise the eyelids; *C*, patient in attempt at right lateral gaze; *D*, patient in attempt at left lateral gaze; *E*, patient in attempt at downward gaze; *F*, patient in attempt at upward gaze.

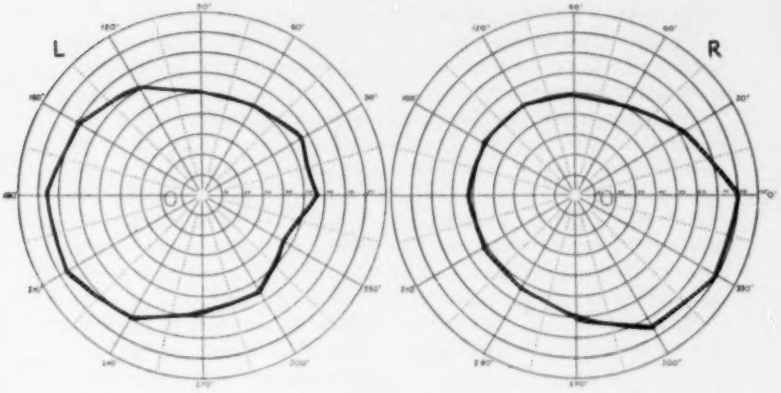

Fig. 6 (case 3).—The peripheral fields for 2/250 white show no remarkable defects.

to droop. Photographs furnished by the family revealed normal, wide open eyes at the age of 7. At the age of 14 a bilateral operation for ptosis was performed, with little or no improvement in the condition.

Examination revealed almost total external ophthalmoplegia, although the patient did not complain of diplopia. Visual acuity was 15/30 in the right eye and 15/50 in the left eye, not correctible with glasses. Scattered areas of pigmentary disturbance appeared throughout both fundi. In some areas the normally orange fundus reflex was only yellowish, with fine deposits of pigment. No bone

corpuscle clumps were seen. While some of these pigmentary changes were near the disk, most of them were at the periphery.

Studies of the peripheral field for 2/250 white showed no contraction of either field.

In addition to these ocular changes, the patient showed some difficulty in talking and swallowing, indicative of bulbar palsy.

Summary.—All 3 patients showed bilateral external ophthalmoplegia, starting at the ages of 11, 12 and 13, respectively, the ptosis being most prominent and appearing early. They also presented atypical pigmentary degeneration of the retina, which was not of the bone corpuscle type. Studies of visual fields under good illumination showed no remarkable impairment of the periphery, the picture thus differing from the so-called primary pigmentary degeneration of the retina, in which the annular scotoma may even precede the appearance of pigment in the fundus.

It is interesting that none of these patients complained of diplopia. The absence of this symptom may have been due, in part, to the pronounced ptosis.

COMMENT

All these features place the 3 cases reported in the same category as the cases of Barnard and Scholz [6] and of Walsh.[7] In addition, in 1 of the cases optic neuritis was present at the age of 14. Considering the infrequency of optic neuritis at this age, it is possible that this condition is part of the same picture.

Walsh suggested that chronic progressive ophthalmoplegia in the presence of a familial history is a clinical entity and that variants are associated with spinal or bulbar palsies, as well as with pigmentary degeneration of the retina. Case 3 of our series was characterized by the chronic external ophthalmoplegia, the bulbar palsy and the pigmentary degeneration, the case thus serving as a sort of link between these variants. It is likely that all these stigmas belong to a general neuroretinal degenerative disorder with many variants.

In view of the fact that the pigmentary changes may be scant and difficult to recognize, it is possible that some of the patients with ophthalmoplegia for whom pigmentary retinal changes have not been reported may actually have had them and that these lesions would have been found if the periphery had been carefully explored with good dilation of the pupil.

From the neuro-ophthalmologist's point of view, the finding of such pigmentary changes can be of great value in clinical differentiation of this syndrome from such conditions as myasthenia gravis and tumors and vascular anomalies at the base of the brain or at the apex of the orbit. While bilaterality is usual, and unilaterality is more likely to denote a mass lesion, there have been reports of unilateral progressive ophthalmoplegia lasting for years before the other eye was involved.

In searching for early or minimal changes in the retina, one should look especially for light yellowish areas, as differentiated from the surrounding dark orange areas. Small, irregular, granular pigment deposits should be differentiated from the more regular, linear appearance of pigment in the periphery of some normal tessellated fundi. If one is in doubt, it is well to compare the area rapidly with other areas equidistant from the disk. In this way, one may detect early changes more easily than by constantly fixing on one small area and attempting to evaluate the intricate details.

When evidence of paralyses of the third, fourth or sixth nerve is present, and when the history, plain roentgenograms, reactions to the neostigmine test and other clinical findings are inconclusive, the presence of pigmentary changes in the retina can be of aid in the diagnosis of a degenerative disease, and thus obviate the necessity of angiography, air studies or other surgical diagnostic procedures.

CONCLUSIONS

Pigmentary degeneration of the retina occurs with external ophthalmoplegia as a degenerative disease.

In all cases of external ophthalmoplegia, especially those in which tests for myasthenia with neostigmine or physical signs of intracranial tumor or aneurysm are lacking, a careful search should be made for early pigmentary degeneration of the retina, the finding of which will help to place the condition in the category of a degenerative disease.

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INFLUENCE OF AGE AND SEX ON FLOW OF TEARS

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IN THE course of a clinical study of keratoconjunctivitis sicca, the question arose as to what constitutes a normal flow of tears. In the search of the literature we found that several authors [1] had postulated certain values as comprising the normal flow of tears during their clinical observations on eyes with keratoconjunctivitis sicca. Schirmer,[2] who originated the test on which most clinical observations are now based, investigated the flow of tears in 100 eyes which he considered normal. He came to the conclusion that a normal person secretes from 0.5 to 0.67 Gm. of tears per day and that more than 15 mm. of wetting in five minutes was normal when his filter paper method 1 was used to determine the flow. Schirmer, however, did not tabulate the results in all of the cases, so that the reader does not know the exact range of values that constituted the normal or the age or sex of the persons examined. DeRoetth [3] was interested in this problem and published some of his conclusions after a study of the flow of tears in 162 patients who were observed during routine refractions. It was his impression that both age and sex were factors in the secretion of tears. Since the factors of age and sex, as well as the flow of tears, seem intimately concerned with the occurrence of keratoconjunctivitis sicca, we felt that further investigation of the interrelation of these factors in persons without ocular disease was indicated.

Dr. Henderson is from the Section on Ophthalmology, the Mayo Clinic.

1. (*a*) Beetham, W. P.: Filamentary Keratitis, Tr. Am. Ophth. Soc. **33**:413-435 (June) 1935. (*b*) Bruce, G. M.: Keratoconjunctivitis Sicca, Arch. Ophth. **26**:945-964 (Dec.) 1941. (*c*) Gifford, S. R.; Puntenney, I., and Bellows, J.: Keratoconjunctivitis Sicca, ibid. **30**:207-216 (Aug.) 1943. (*d*) Sjögren, H.: A New Conception of Keratoconjunctivitis Sicca: Keratitis Filiformis in Hypofunction of the Lachrymal Glands, translated by J. Bruce Hamilton, Sydney, Australia, Australasian Medical Publishing Company, Ltd., 1943.

2. Schirmer, O.: Studien zur Physiologie und Pathologie der Tränenabsonderung und Tränenabfuhr, Arch. f. Ophth. **56**:197-291 (June) 1903.

3. deRoetth, A.: On the Hypofunction of the Lacrimal Gland, Am. J. Ophth. **24**:20-25 (Jan.) 1941.

METHODS

The subjects chosen for this study were patients at the Mayo Clinic who were undergoing routine ophthalmoscopic examinations. Patients who were selected for study of the flow of tears had neither complaints referable to the eyes nor obvious disease of the eyes. Three persons of each yearly age from 30 through 55 and of each sex were examined. A total of 231 patients (462 eyes) were examined. Of these patients, 114 were males and 117 were females. The ages of the males ranged from 16 through 67 years and those of the females from 16 through 66 years.

The method selected for the measurement of the tears in the conjunctival sacs of these subjects was essentially the same as method 1 devised by Schirmer [3] and described in the textbooks of Gifford [4] and Duke-Elder [5] and in the writings of Bruce,[1b] Beetham [1a] and deRoetth.[6] All investigators who have worked with this test have realized the inherent inaccuracies of the procedure, but a more practical method has not yet been devised so far as we have been able to ascertain. In an attempt to overcome some of these inherent defects, various modifications of the original test have been proposed, such as the use of litmus paper instead of filter paper, the performance of the test with the eyelids closed instead of open, the utilization of special filter papers of certain texture and absorbability and the placing of the strips of filter paper at various positions along the margins of the lower eyelid instead of close to the inner canthus, as well as modifications designed to change the length, width or contour of the filter paper.

Realizing the difficulties of performing the exact procedures on successive subjects, we attempted to be as uniform as possible (1) by utilizing filter paper of standard length and width (30 by 5 mm.) from the same manufacturer's lot; (2) by hooking the proximal 5 mm. of filter paper over the portion of the margin of the lower eyelid adjacent to the punctum lacrimale in each case and (3) by having one of us (W. A. P.) conduct all of the testing procedures. As in the procedure originally proposed by Schirmer, that portion of the filter paper not in contact with the palpebral conjunctiva which was moistened in five minutes was considered to represent the measurement of the flow of tears. In several instances the entire strip of filter paper was moistened in less than five minutes, so that for the given period the amount of tear flow would be somewhat greater than 25 mm.

RESULTS

The results of these testing methods for the females and for the males, respectively, are shown on the scatter graphs (charts 1 and 2). In these graphs the flow of tears up to 26 mm. is represented on the ordinates, and the ages of the patients are plotted on the abscissas. Each unit on these graphs represents the tear flow of one eye.

On first glance at these scatter graphs, one is impressed with the variability of tear flow in apparently normal eyes. Among the females, as shown in chart 1, from the approximate ages of 30 to 60 years there

4. Gifford, S. R.: A Hand-Book of Ocular Therapeutics, revised by Derrick Vail, Philadelphia, Lea & Febiger, 1947.

5. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

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is a scattering of units representing almost every degree of tear flow. Among the males, as represented by chart 2, there is a similar scatter of results except that it seems limited somewhat to the approximate ages of 30 to 55 years. For persons of each sex there seems to be a tendency for the majority from 16 through 29 years of age to have a tear flow

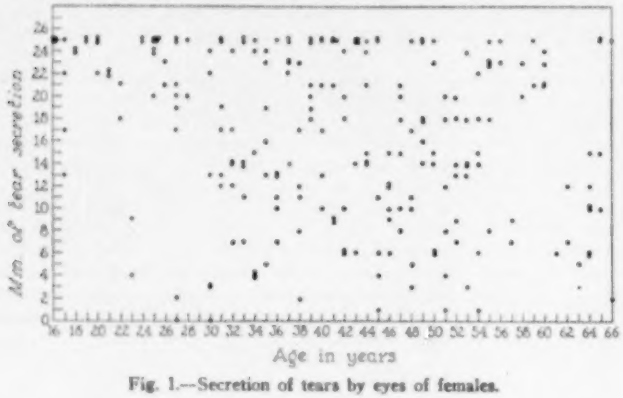

Fig. 1.—Secretion of tears by eyes of females.

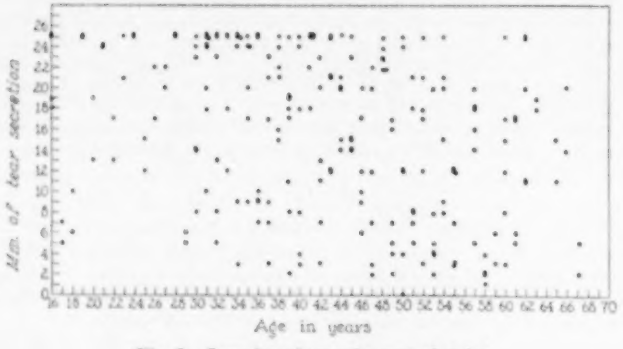

Fig. 2.—Secretion of tears by eyes of males.

represented by units confined mostly to the upper third of the values represented by the ordinates. On the other hand, there seems to be a tendency among the older members of each sex (women beyond the age of 60 and men beyond the age of 55) to have a flow of tears represented by units in the lower half of the values represented by the ordinates. In other words, from a study of these figures the impression is gained that up to the age of 30 the quantity of tears is fairly consistently higher

than it is beyond a certain age (55 for men and 60 for women). For the middle age groups values are so variable that it is nearly impossible to postulate what flow of tears may be expected in any given case. Furthermore, it might be assumed from a brief survey that there is little difference in the values for each sex, and only if the young adults are compared with the more elderly subjects can there be said to be a definite drop in the average flow of tears.

For convenience of study, and to ascertain whether these first impressions were correct, the statistical data gathered concerning per-

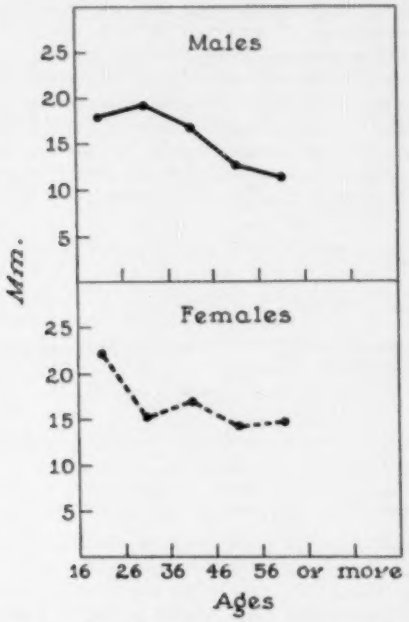

Fig. 3.—Average secretion of tears by eyes of persons of various age groups.

TABLE 1.—*Mean Values for Flow of Tears of Persons of Each Sex According to Decades*

Age, Years	Males		Females	
	Number of Eyes Tested	Average Tear Flow, Mm.	Number of Eyes Tested	Average Tear Flow, Mm.
16-25	22	18.0	32	22.1
26-35	46	19.1	50	15.3
36-45	62	16.8	60	17.0
46-55	60	12.6	60	14.3
56 or more	38	11.5	32	14.6

sons of each sex were studied from the standpoint of age by decades and arbitrary ranges of tear flow.

In table 1 are recorded the results when mean values for the flow of tears of persons in successive age decades were calculated. These data indicate a definite tendency for the flow of tears to decrease with advancing age. No significant difference is evident in the two sexes in this respect, for the amount of decrease in flow of tears from the first decade tabulated up to and including the last decade tabulated was practically the same for the two sexes; that is, 6.5 mm. for males and 7.5 mm. for females. When the span of ages from 16 through 67 years is considered, this total decrease of only 6.5 to 7.5 mm. of wetting

TABLE 2.—*Percentage Incidence of Flow of Tears for Males in Each Decade*

Flow of Tears in 5 Minutes, Mm.	Percentage Incidence by Age, Years				
	16-25	26-35	36-45	46-55	56 or More
0- 5	4.5	6.5	8.0	25.0	31.5
6-10	13.6	13.0	14.5	20.0	10.5
11-15	18.1	8.6	20.2	15.0	21.0
16-20	18.1	15.2	17.7	10.6	28.9
21-24	13.6	21.7	19.3	10.6	0.0
25 or more	31.8	34.7	20.0	6.6	7.8

TABLE 3.—*Percentage Incidence of Flow of Tears for Females in Each Decade*

Flow of Tears in 5 Minutes, Mm.	Percentage Incidence by Age, Years				
	16-25	26-35	36-45	46-55	56 or More
0- 5	3.9	20	5.0	10.0	9.3
6-10	3.0	4	18.3	22.3	34.3
11-15	2.0	24	20.0	20.6	12.5
16-20	9.3	18	11.6	21.6	6.2
21-24	28.1	18	16.6	11.6	21.8
25 or more	53.1	16	28.3	6.6	15.6

of the filter paper does not seem to be very definite or significant. If the eyes tested were normal, as they seemed to be, there appears to be little significant clinical difference in the flow of tears from normal eyes at any age. In study of the data included in table 1, it must be remembered that the mean values for each decade only approached the true average value, for the length of the testing agent (25 mm.) necessarily prevented some subjects from exhibiting a greater flow of tears.

Further perusal of the data presented in chart 3 and in table 1 reveals that on the basis of mean values females tended to have a slightly higher flow of tears than males in all age groups except between that from 26 through 35 years. We are unable to explain this reversal of the trend in this particular decade.

In tables 2 and 3, the total range of flow was arbitrarily divided into groups representing 5 mm. of increasing value, and the percentages of persons falling into the respective groups were tabulated. In the data

tabulated for the males (table 2) there is an apparent uniform tendency for the secretion of tears to decrease in direct proportion to the advancing age. Although there is a similar tendency for the flow of tears to decrease with age among females, as noted in table 3, the trend is more fluctuant and cannot be said to be directly proportional to increasing age. For the females of several decades there is a fairly equal distribution of subjects throughout the ranges of tear flow. For a person of any given age, then, it would be more difficult to estimate the expected secretion of tears if the subject were female rather than male.

This statement, however, holds true only for women after a certain age, for reinspection of the data in table 3 and of the scatter graph (chart 1) reveals that a surprising majority of young women possessed a high numerical average for the tear flow. In only 5 (11 per cent) of 44 eyes of 22 women examined who were less than 30 years of age was the tear flow less than 17 mm. in five minutes. In 35 eyes (80 per cent) the tear flow was 20 mm. or more in five minutes. It seemed reasonable to predict, then, that the majority of women less than 30 years of age will possess a tear flow of 20 mm. or more in five minutes, and this estimate probably approaches normal if it is possible to say that a normal exists.

On the other hand, beyond the age of 60 (chart 1) only 3 of the 20 eyes of the women examined had a tear flow of more than 20 mm. in five minutes, and 80 per cent (16 eyes) of this age group exhibited a flow of tears of 15 mm. or less in five minutes.

Among the males (chart 2) a similar situation does not exist except that 80 per cent (23 of the 28 eyes examined) of the eyes of persons less than 30 years of age had a tear flow of 13 mm. or more in five minutes.

In an attempt to determine whether the time of day influenced the rate of tear flow, we carefully noted the hour at which the tests were performed. Since our examinations were performed only between the hours of 8 a. m. and 5 p. m., we cannot come to any conclusion concerning the diurnal fluctuation of the flow of tears. However, within the time limits of our tests, we concluded that the hour of the day has no influence on the rate of tear flow.

Since we were concerned with several aspects of what might be said to be a normal flow of tears among persons representative of various ages and of the two sexes, we reviewed our data to ascertain whether there were any differences in the flow of tears from a pair of eyes. Because we were testing apparently normal eyes, it might be assumed that the secretion from the two eyes would be equal, or nearly so. We found this to be true only within certain limits. Fifty-six per cent of the females and 57 per cent of the males exhibited a difference of 3 mm. or less in the wetting of the strips of filter paper in five minutes for a given pair of eyes. Another 12 per cent of the females and 11.5 per cent of the males produced a difference of 4 and 5 mm. of wetting of the strips of filter paper for their pair of eyes. Thus, about

68 per cent of subjects, whether they were females or males, had a difference of 5 mm. or less in the flow of tears from their two eyes, and usually each eye approached its fellow eye in this respect to within 3 mm. by the testing methods employed. A difference of 3 mm. or less for a given pair of eyes had been looked on as normal from our clinical experience with this test and before this study was undertaken. However, we were surprised that about 32 per cent of persons were likely to have a difference of more than 5 mm. in flow of tears from their eyes. This pronounced difference in the flow of tears from a given pair of normal eyes cannot be readily explained unless it be due to the inherent errors of the testing methods.

COMMENT

As pointed out previously, several other investigators have been interested in the normal rate of flow of tears since Schirmer [2] described his method of measurement and concluded that less than 15 mm. of wetting in five minutes was pathologic. Beetham,[16] after using the Schirmer method, found that several normal-appearing patients possessed a tear flow as low as 10 mm. in five minutes and proposed that this amount, rather than Schirmer's original figure, be considered the lower limits of normal. Gifford, Puntenney and Bellows,[15] while working on the problem of keratoconjunctivitis sicca, observed that some patients possessed a tear flow of less than 5 mm. in five minutes without showing any signs of ocular disease. They [15] observed some of these patients for periods of six to twelve months without noting any change in the eyes or in the rate of tear flow. In our own group of patients, we found that the flow of tears in about 10 per cent of the eyes of the females and in about 16 per cent of the eyes of the males tested was 5 mm. or less. This finding would confirm the impression gained by Gifford, Puntenney and Bellows [15] that some apparently normal persons possess a tear flow that is much less than that which has heretofore been considered normal. Furthermore, our findings would make it difficult to propose an exact limit of normal, as did Schirmer and Beetham, for between the ages of 30 and 60 years among the women and the ages of 30 and 55 years among the men, the results were much too variable. DeRoetth [8] in his study of 162 normal persons, concluded that the lacrimal secretion of a third of his patients who were more than 40 years of age would be considered pathologic by Schirmer; de-Roetth's [8] observations therefore also tend to support the contention that an exact limit of normal would be difficult to determine. In our own series, about 50 per cent of both women and men more than 40 years of age secreted less than 15 mm. of tears in five minutes.

DeRoetth [8] also concluded that lacrimal production decreased with age, thus confirming Schirmer's original observation that younger persons have more tears than older ones. Our findings tend to support these conclusions, and, in general, the decrease in flow of tears was in inverse proportion to the increase in age. However, in our study the

average decrease between the ages of 15 through 68 years was so slight (6.5 to 7.5 mm.) as not to seem of much clinical significance, particularly in view of the difficulties in establishing a norm.

In his studies, deRoetth [8] found that young women have more active lacrimation than young men and that older women produce a smaller amount of tears than older men. With these conclusions we tend to agree. Our survey of males and females between 15 and 30 years of age revealed a definitely higher flow of tears among the females. Beyond 60 years of age the women exhibited a lower average flow of tears than the men of corresponding ages, but the difference was so slight as to be of doubtful statistical significance.

SUMMARY

The eyes of 231 patients (114 males and 117 females) were examined to determine whether the factors of age and sex influenced the flow of tears.

A modification of the testing method of Schirmer was used in collection of the necessary data. It should be kept in mind that the interpretation of data based on this test is influenced by certain variables and inherent defects in the testing procedure.

In general, it was not possible to determine the normal rate of flow of tears for persons of either sex older than 29. Among females of 15 through 29 years of age a flow of tears of 20 mm. or more in five minutes seemed to be normal. Among males of 15 through 29 years of age a flow of tears of 13 mm. or more in five minutes seemed to be normal.

Age seems to be an influencing factor on secretion of tears, as was indicated when values for patients of successive decades were compared. In general, the decrease in flow of tears was roughly parallel to the increase in age. The total decrease in the mean values for patients from the age of 16 through 68 years was not very marked, however, and was of doubtful clinical significance.

Sex was not a factor in the rate of flow of tears except among young persons (16 through 29 years of age) and persons beyond 60 years of age. In the former group, females exhibited a definitely greater flow of tears than males, and in the latter group women seemed to have a smaller flow of tears than men, although the difference was slight.

The majority of persons tested showed a difference of 3 mm. or less in the flow of tears from their two eyes.

Between the hours of 8 a. m. and 5 p. m. no diurnal influence was noted in the flow of tears.

THE TUOHY CORNEAL LENS

A Second Report

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LOS ANGELES

SUFFICIENT time has elapsed and enough additional patients have been fitted with the corneal lens to warrant a second report.[1] Approximately 600 patients have been fitted to date, and the results are promising. The Tuohy corneal lens [2] appears to have established itself as another mechanical aid to vision. How widespread its use will become cannot be determined until more time has passed and other ophthalmologists have reported on it.

The Tuohy corneal lens does not require any accessory foreign solution but makes use of the patient's own lacrimal fluid. It has no scleral flange and consists only of a corneal part, which rests within the limbal circumference. It should be emphasized at this point that extreme accuracy is required in determining the lens to be prescribed, as the amount of error tolerated is very small. The lens must be clean and well wetted when applied. These points will be dealt with more fully in the discussion on fitting.

THE TUOHY CORNEAL LENS

At present the corneal lens is made of methyl methacrylate. Button-like blanks of this plastic are cut and polished to produce a series of inside curvatures applicable to corneal curvatures, as measured with an ophthalmometer. The stock series of inside curvatures numbers twenty-seven in all, the radiuses of curvature ranging from 7.50 to 8.80 mm., in differences of 0.05 mm. If lenses of longer or shorter radiuses of curvature are required, these are made as a special order. Clinical trial has shown that over 75 per cent of patients can be fitted from the stock series.

The plus or minus spherical dioptric power is cut and polished on the outside surface in 0.25 D. differences. No cylinder is embodied in the lens because corneal astigmatism is corrected by the layer of lacrimal fluid which is present beneath the lens by reason of capillarity. This

1. The first report was published in the *Annals of Western Medicine and Surgery* (2:241 [June] 1948).

2. This plastic lens owes its origin to Mr. K. M. Tuohy, technical assistant, department of ophthalmology, College of Medical Evangelists, Los Angeles.

ever present layer of lacrimal fluid is referred to as the lacrimal lens, or the lacrimal lens factor, and always has a minus dioptric value. It is thinner at the center than at the periphery because the inside base curve of the corneal lens chosen is approximately 0.30 mm. longer than the radius of curvature of the cornea in its longest meridian, as obtained from the ophthalmometer readings. It can therefore be seen that the radius of curvature of the longest meridian of the cornea and the radius of curvature of the lens to be used being known, the minus dioptric value of the lacrimal lens is readily computed. A complete table has been set up for this purpose.

Because the lacrimal lens has a minus dioptric value, all cylinders in the spectacle prescription are transposed to minus cylinders and then disregarded. The total spherical part of the spectacle correction only then becomes a significant and important measurement.

Another important feature of the Tuohy corneal lens is its marginal bevel of the inside curve. This increases the separation of the periphery of the lens from the periphery of the corneal epithelium and thus increases toleration by preventing contact. It also permits any periodic overriding at the limbus without contact. The bevel promotes the formation of the lacrimal lens, its continued presence and its circulation, which is so vital[5] to corneal respiration, as well as the correction of corneal astigmatism and corneal irregularities (as in cases of conical cornea). Lenticular astigmatism is not correctable with the Tuohy corneal lens.

The lens has a diameter of 11 mm. in its regular size. Only occasionally is it found necessary to use a lens with a longer or a shorter diameter. Large corneas and those not having a definite limbal sulcus do better with a lens of larger diameter, 11.5, or even 12 mm. depending on the individual case.

MEASUREMENTS REQUIRED TO OBTAIN THE CORRECT CORNEAL LENS

The first step is to obtain the spectacle prescription with or without cycloplegia, as indicated. The second is to measure the vertex distance in all cases in which the spectacle prescription, transposed to a minus cylinder, has a spherical value of 5 D. or more. As already mentioned, the minus cylinder is disregarded in estimating the corneal lens required. The vertex distance should be taken for each eye. For this purpose, I prefer to use a stenopaic plastic lens and metal millimeter rule. A table of vertex distances is used in estimating the dioptric power effect such distance has on the spectacle correction; again, a complete table has been compiled.

The third, and last, measurement is the ophthalmometer reading. This should be carefully made and should represent a mean average of

at least three trials for each principal meridian. The ophthalmometer readings give the logical starting point for choosing the inside curve to be used. This curve having been chosen and the longest radius of curvature of the cornea being known, the lacrimal lens factor is then computed or taken directly from the prepared table and its minus value included in arriving at the total dioptric power required.

In practice, three pairs of lenses are chosen for the first trial: the first pair being arrived at by the deductions outlined, the second pair having an inside radius of curvature 0.05 mm. longer than the radius of curvature of the first pair and a third pair having an inside radius of curvature 0.5 mm. shorter than that of the first pair. This is advisable because of the variability of ophthalmometer readings. However, the spectacle correction, the vertex distance and the ophthalmometer readings form only the basis on which these first lenses are ordered. This saves the examiner the task of random trail of twenty-seven different inside curvatures. These measurements also give an approximation of the vision to be expected with the final lens, and this is an advantage during the fitting period.

THE FITTING PROCEDURE

The fitting of the lens must be preceded by examination of the cornea with the slit lamp for the purpose of subsequent comparison.

The lens chosen for trial must be cleaned and well wetted with any one of the accepted germicidal wetting agents before being applied to the cornea. A germicidal wetting agent marketed by Barnes-Hind Laboratories is one that has proved adequate. Ordinary household detergents are also satisfactory for wetting. The wetting agent should be rinsed carefully from the lens with a 2 percent solution of sodium bicarbonate, distilled water or tap water before the lens is applied. An ophthalmic atomizer is useful for this purpose. Some patients use their own saliva for wetting; this practice, however, cannot be recommended in spite of its practicability.

The wetted lens is gently placed over the cornea with the index finger or the suction cup (no suction is used). At the first trial excessive lacrimation may occur, and the patient will complain of discomfort beneath the upper lid. One should ascertain by trial which of the three chosen pairs of lenses is the most comfortable and permit the patient to wear these for one hour. On the second day a wearing for two hours is advised, and on the third day, a wearing for three hours.

A second examination with the slit lamp, aided by fluorescein, is of the utmost importance. This inspection will show clearly the presence, depth and distribution of the lacrimal lens. Mucous shreds and minute bubbles enhance this visualization. If any abrasion occurs at the corneal apex, the lens with the radius of curvature 0.05 mm. shorter than that

previously used, is tried in order to obtain more apical clearance. If such an abrasion should occur peripherally, the lens with the radius of curvature 0.05 mm. longer is tried in order to obtain more peripheral clearance. These clearances can be roughly estimated by observing the density of the fluorescein beneath the lens.

When the examiner is satisfied that he has obtained the correct inside curvature, he then proceeds with a secondary manifest refraction. Spheres only are required for this because lenticular astigmatism cannot be corrected with the corneal lens. Usually 0.25 to 0.5 D. of lenticular astigmatism will be present (against the rule), but this must be disregarded and the best visual acuity obtainable with spheres accepted. This added requirement, if present, is obtainable in a new lens which has the same inside curvature as that previously established as correct. The new lens will have the corrected dioptric power on its outside curvature.

The patient must be carefully instructed as to cleanliness, wetting, inserting and removal of the lenses. Gentleness, as well as the confidence of the patient, is of prime importance if blepharospasm is to be reduced.

When the examiner has the correct and final lens and the patient is adequately trained, slow and steady increase in toleration is then begun. The corneal epithelium seems to "toughen," not as a clinical manifestation, but as an adaptability, and this process cannot be hurried. It is faster in some patients than in others, for no known reason.

As can be seen, much care is necessary, and repeated observation is recommended until more is known about this new lens. The patient should be given examination with fluorescein and the slit lamp at regular intervals for many months, so that complete data may be accumulated and full reports presented. Much of the foregoing procedure may become unnecessary later, but at present it behooves us as ophthalmologists to act cautiously, so that we may learn more about this entirely new procedure.

COMMENT

Statistics on the 600 patients fitted to date are not yet available and cannot be included in this report. The majority of the patients are scattered over Southern California, and the fitting has been done by at least thirty-five men. This, together with the fact that the lens itself is only a little over a year old and that all but 12 of the patients have been fitted within the past six months, is ample reason that complete statistics are not available. However, in general, the Tuohy corneal lens appears to be far superior to any of the contact lenses previously used.

My series of 50 patients are still under study. It is possible that the results for 5 of these will be termed failures because of excess irritation and poor toleration. It is difficult at this time to estimate of what failure consists because it is easy to obtain wearing time of six or more hours.

Many patients will wear their lenses all day if permitted to do so, but this is not necessarily the correct procedure until the patient has been under observation for a longer period. Minor corneal abrasions occur if the fit is poor, if blepharospasm is present or if the increase in wearing time has been too rapid for corneal "toughening" to develop. This corneal "toughening" is an important factor and has a great deal to do with toleration, because it lessens the possibility of abrasion and helps prevent imbibition of the patient's own lacrimal fluid. If imbibition occurs, it can be seen by the sclerotic scatter method of illumination and biomicroscopy.

Adequate circulation of the lacrimal lens for the purpose of corneal respiration is also of great importance and is made possible by capillarity. This lacrimal lens is maintained by correct fit of the corneal lens and by movements of the lids without undue blepharospasm.

The extensive imbibition of fluid, as observed with the biomicroscope, after the wearing of the old type of contact lens is not seen with the corneal lens. Imbibition of fluid does occur, but it is infrequent and minimal by comparison. Corneal staining with fluorescein after the wearing of the old type of contact lens was a frequent finding, and staining may also occur with the corneal lens, particularly if the fit is poor, blepharospasm is present or the wearing time is increased too rapidly.

It is well to mention at this point that best results are obtained when the cornea being fitted has a definite limbal sulcus, as this helps to maintain the position of the lens. Conversely, if the corneal curvature merges with the scleral curvature without a definite limbal sulcus, the corneal lens tends to ride too freely.

The patient must be cooperative and willing to follow the advice given. He must return repeatedly for careful study by means of the slit lamp with fluorescein. Significant corneal abrasion is known to have occurred in 1 patient. This patient did not return for follow-up observation but persisted in wearing the lenses throughout his waking hours from the first day that they were entrusted to him. Fortunately, healing was rapid and absorption of infiltrate excellent.

The Tuohy corneal lens is not meant to take the place of spectacles. Time and trial will establish its usefulness in vocational and occupational fields, and its use for cosmetic purposes cannot be denied.

The ideal length of wearing time has not been established. Many have worn the lenses every day through all their waking hours for many months without showing any corneal abrasions or changes. Others cannot do this so easily and find that their toleration time is much less. However, it can be said that an eight hour average is easy to obtain for the majority. I prefer my patients to remove the lenses at every reasonable opportunity until I have had more time to observe the

development of this lens. It must be stated that the patient is often more comfortable with the lens on if any corneal abrasion exists, and therefore this complication may be masked.

Not all the factors that mean success in wearing this new lens are known, but consideration must be given to such things as too tight a fit, too loose a fit, imbibition of lacrimal fluid by the corneal epithelium, sensitivity to the plastic, blepharospasm, cleanliness, wetting and foreign bodies or chemical irritants in the lacrimal lens.

The Tuohy lens is still in its infancy, and conclusions at this stage are not necessarily correct. The principle embodied in this lens has created a new approach to the problem of correction of the high refractive errors—the conical cornea and aphakia. Thus far it has shown promise for each of these conditions. Originally it was felt that the mechanical difficulties would be too great in fitting the conical cornea. This has since proved wrong, as 20 patients with keratoconus have been fitted with a high degree of success. Fitting the conical cornea requires greater experience, for the ophthalmometer cannot be depended on to nearly the same extent, as it gives only a rough estimate of the starting point in choosing the inside radius of curvature. The dioptric range in all types of cases corrected to date is from + 18 to —22 D. and for cylinders up to 8 D.

The necessary procedure for prescribing and fitting this new lens is much easier than that required for the older type of contact lenses, but the follow-up study must be a great deal more accurate. The margin of error between success and failure is extremely small, and accuracy therefore is of paramount importance.

More work and observation are necessary, and the field of new plastics is to be explored.

SUMMARY AND CONCLUSION

A new mechanical aid to vision, namely, the Tuohy corneal lens, has been further reported on.

It appears to have established a new concept and is ready to take its place among other aids to vision. How widespread its use will become depends on the accuracy of all measurements and the proving of its safety.

It appears to be superior to the older types of contact lenses so far as comfort, blurring (imbibition) and wearing time are concerned.

Experience is essential in fitting, and the successful examiner is one who is willing to repeat his measurements on the least provocation.

More cases are required for statistical purposes, more time is needed for observation and the results of other ophthalmologists must be reported before the part the Tuohy corneal lens will play in the correction of visual errors can be established.

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OCULAR PEMPHIGUS

Report of a Case

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THE TERMS ocular pemphigus and pemphigus conjunctivae are synonymous and designate a type of pemphigus of the mucous membranes. Ocular pemphigus may be defined as a chronic, slowly progressive disease of the epithelial coat of the eye, which ultimately leads to cicatrization. It frequently is associated with vesicular lesions of the mucous membranes and sometimes with cutaneous lesions. In contrast to other forms of pemphigus, it runs a benign course as concerns the life of the patient and is usually devoid of constitutional symptoms. The etiologic agent is unknown, but the theory of a toxic origin is favored.

Pemphigus is classified as acute pemphigus vulgaris, chronic pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus (Senear-Usher disease) and pemphigus of the mucous membranes. Cowan and Klauder [1] maintained that pemphigus of the mucous membranes should be considered a distinct entity and should further be distinguished from the essential shrinkage or shriveling of the conjunctiva of von Kries [2] and from the scarring of the conjunctiva accompanying a number of dermatologic diseases characterized by bleb formation.

The incidence of ocular pemphigus is variously put at from 1 in 9,000 ophthalmic patients (Franke [3]) to 1 in 75,000 (Posey [4]). There is considerable question of the correct diagnosis of ocular pemphigus, and it is probable that the incidence is greater than reported. According

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to an analysis by Lever and Talbott [5] about 16 per cent of all cases of pemphigus are ocular. The incidence is greater in females, but there is no racial difference. The disease has been seen in all age groups after the second decade of life.

The pathologic picture is not pathognomonic. Parsons [6] stated that there is early conjunctival swelling due to edema, swelling of fibrous tissue and lymphoid infiltration. Later, the conjunctival epithelium is thickened and sends coarse pegs into the subconjunctival tissue. There are thick infiltration of the submucosa with round and spindle-shaped cells, enormous hypertrophy of fibrous tissue and increased vascularity.

There is no laboratory phase of the disease. Although Lever and Talbott [7] observed changes in the blood serum in cases of acute and chronic pemphigus vulgaris and pemphigus vegetans, no abnormalities of the serum are associated with the ocular type. Pels and Macht [8] devised and standardized a test in which seedlings of Lupinus albus show reduced root growth in a nutrient solution to which the blood serum or contents of bullae of pemphigus is added. The test gives positive results for all types of pemphigus, including the ocular type.

The symptoms of ocular pemphigus are not specific. The first signs are those of purulent conjunctivitis, which may yield various bacteria. Later, the conjunctival injection becomes chronic; there is slow reduction in lacrimation, and a ropy, sometimes foamy, secretion is prominent. Conjunctival scarring of all types develops insidiously, and without noticeable inflammation. Cicatricial contractions develop in all conceivable forms, but a common occurrence is symblepharon at the inner canthus extending beyond, and thus obscuring, the punctum. The cornea may be covered with a cuticular membrane, which diminishes, or even destroys, vision. Ankyloblepharon may occur and proceed to loss of the globe.

The skin may be involved for several years before, or simultaneously with, the eyes, or cutaneous lesions may follow those of the eyes, even after a long period.

The treatment of ocular pemphigus is still unsatisfactory. The more favored remedies are arsenicals and the vitamins. A study by Lever and Talbott [7] showed encouraging results with adrenal cortex

5. Lever, W. F., and Talbott, J. H.: Pemphigus: A Clinical Analysis and Follow-Up Study of Sixty-Two Patients, Arch. Dermat. & Syph. **46**:348 (Sept.) 1942.

6. Parsons, J. H.: The Pathology of the Eye, London, Hodder and Stoughton, Ltd., 1904, vol. 1, pp. 89-91.

7. Lever, W. F., and Talbott, J. H.: Pemphigus: A Further Report on Chemical Studies of the Blood Serum and Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D, New England J. Med. **231**:44 (July 13) 1944.

8. Pels, I. R., and Macht, D. I.: Phytopharmacology of Pemphigus and Other Dermatoses: Additional Studies, Arch. Dermat. & Syph. **23**:601 (April) 1931.

extract and dihydrotachysterol in all types of pemphigus except the ocular type. Choline as a wetting agent to the eyes has been recommended. Surgical treatment, either by separation of scar formation or by transplantation of normal mucous membrane, is unsatisfactory.

The infrequent incidence of this disease prompts the report of a case with unusual features not previously noted in the literature. A biopsy of the conjunctiva was made.

REPORT OF CASE

A white man aged 30 noted his first symptoms in June 1947. There was transient diplopia, followed by signs and symptoms of conjunctivitis and blisters

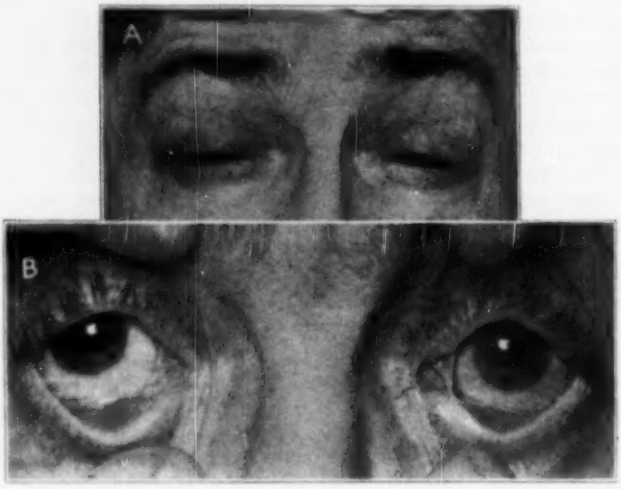

Fig. 1.—*A*, cicatricial ptosis and entropion, which were present on admission. *B*, general contraction of cul-de-sacs and symblepharon of inner canthi. Bilateral pannus shows faintly.

in the mouth. Within the next two days the blisters of the mouth had become very painful, and swallowing was difficult. In a few days blisters appeared over the back of the neck, over both upper arms, both surfaces of the hands and the plantar surfaces of the feet. He entered a hospital with a temperature of 102 F.; the fever did not persist, and the illness was not prostrating. By that time bullae had appeared over the chest and on the left side of the abdomen, the penis and the scrotum. He was hospitalized for about five weeks, during which time treatment was palliative and the dermatitis subsided. He was readmitted a month later for treatment of conjunctivitis sicca. During and after the second hospitalization peeling occurred. The patient stated that all of his finger nails were lost at that time.

The patient was admitted to this hospital on Oct. 28, 1947, showing the effects of recent loss of weight.

Physical examination showed a small vesicle about 2 mm. in diameter just inside the lower lip and several pigmented areas in the skin and mucous membranes at the sites of old, healed bullae. There was longitudinal scarring of all the finger nails.

Vision in each eye was 20/50 and could not be improved by correction. Photophobia and blepharospasm were noted. The palpebral and bulbar conjunctivas were hyperemic, and the lower cul-de-sacs contained a gray-white, stringy discharge. Both corneas were involved in the disease process. There was a general diffuse, superficial haze with a few small superficial vesicles on both corneas and widespread punctate staining, more marked in the lower half. Superficial limbal blood vessels were encroaching on the corneas. The conjunctiva did not stain, and no blebs were noted on his admission. The disease was limited to the eyelids, conjunctiva and cornea of both eyes. Extensive laboratory examinations contributed only the presence of eosinophilia, with a count of 1 per cent. The basal metabolic

Fig. 2.—Right eye showing tarsobulbar symblepharon and faint corneal opacity.

rate was —4 per cent. Series of cultures and smears were obtained from the conjunctivas. On his admission Pseudomonas aeruginosa (Bacillus pyocyaneus) was obtained. After treatment had been instituted, Corynebacterium xerose, an unidentified gram-negative bacillus and Staphylococcus albus were recovered. An autogenous vaccine was made from the Staph. albus.

Our treatment was corrigent and included use of moist chambers, artificial tears, antibiotics and antiseptics. The Schirmer test showed progressive reduction in tear secretion. Considerable relief was obtained by closing the puncta by cautery. Adhesive tape over the upper eyelids and brow and a pair of crutch glasses were used to alleviate the entropion and blepharospasm.

Several forms of special therapy were given, without noticeable effect. Sulfathiazole was not tolerated, and pilocarpine administered by mouth produced no increase in lacrimation. A decreasing degree of vaccinoid reaction followed inoculations with smallpox vaccine at weekly intervals.

There was no aggravation of his condition with treatment. A crop of three oral blisters appeared shortly after his admission and disappeared within a month, but

the blister on the lip noted on admission remained fifteen months. He left the hospital after a course of treatments with autogenous Staph. albus vaccine had been started, and five months after admission.

During the thirteen months since his discharge his general health has remained the same. Loss of weight has not been regained. There has been no change in appearance of the epidermal scars except for blanching of pigmented areas.

Fig. 3.—Crutch glasses in place to relieve ptosis.

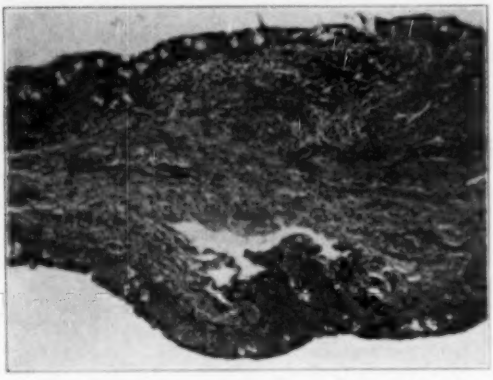

Fig. 4.—Biopsy of conjunctiva from symblepharon of the left eye; × 75.

The eyes have exhibited an insidious progression of symblepharon, a steady growth of pannus and increasing deep vascularization. The corneas have shown an ever shifting, but ever present, punctate staining, more intense in the lower halves, with occasional true blisters, sometimes as many as ten to twenty on one cornea. On one occasion a blister of the cornea near the limbus was matched by a similar blister on the adjacent conjunctiva. Microscopic examination of a piece of tissue taken from an area of symblepharon over the left internal canthus showed the pathologic picture ascribed to ocular pemphigus.

Pathologic Report.[9]—A section of conjunctiva showed the normal stratified epithelium covering most of the specimen. At one end, the epithelium was definitely squamous, with a well developed stratum granulosum and a superficial stratum corneum of flattened, keratinized cells. There was loss of papillary projections. In the remainder of the epithelium were numerous goblet cells. The substantia propria consisted of fibrous connective tissue with hyaline degeneration. There were numerous dilated and congested capillaries. Throughout the substantia propria and in an occasional focus within the epithelium was marked infiltration with lymphocytes, plasma cells, a few neutrophils and a rare eosinophil. No blebs or ulcerations were noted.

DIAGNOSIS

In making a diagnosis of ocular pemphigus, several diseases had to be excluded. Congenital diseases, such as epidermolysis bullosa, have their onset at an earlier age. Diseases due to chemical actions, drug sensitivity and vaccination are usually of shorter duration and would have shown exacerbation with the therapy employed. In the absence of tarsal follicles and typical pannus trachoma was not considered.

Erythema multiforme could not be excluded during the early stages of the disease because of the sudden febrile onset. The acute inflammatory changes in the mucous membranes with bleb formation are common to both erythema multiforme and ocular pemphigus. Richards and Romaine,[10] in reporting a case of purulent erythema exudativum multiforme (Stevens-Johnson disease) which closely paralleled the present case, even to scarring of the nails, excluded a diagnosis of pemphigus because there were no successive crops of vesicles. The Pels-Macht test was not used. The clinical symptoms were ultimately specific for pemphigus.

SUMMARY

A case is reported of bilateral ocular pemphigus which is running a typical chronic course with progressive cicatricial changes involving the palpebral and bulbar conjunctivas. Successive crops of corneal and conjunctival vesicles were associated with diffuse punctate corneal staining and superficial light opacities. There was early involvement of the skin, of short duration. The oral mucous membrane had two crops of vesicles. A normal eosinophil count and the pathologic report of a biopsy specimen from the conjunctiva are in keeping with this diagnosis. An unusual occurrence was the exfoliation of the finger nails with replacement by scarred nails. Diplopia was the first symptom and may be explained on the basis of toxicity. At the time of this report, the ocular disease is still present and is slowly progressive. The patient continues to be under observation.

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9. Report from the Pathology Laboratory, Crile Veterans Administration Hospital, Cleveland.

10. Richards, J. M., and Romaine, H. H.: Keratoconjunctivitis Sicca: A Sequel to Purulent Erythema Exudativum Multiforme (Stevens-Johnson's Disease), Am. J. Ophth. **29**:1121, 1946.

OCULAR INVOLVEMENT IN ERYTHEMA MULTIFORME

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WHEN INVOLVEMENT of the mucous membrane accompanies erythema multiforme bullosum, serious ocular sequelae may occur. Of 162 previously reported cases of erythema multiforme with mucosal involvement, the eyes were affected in 148. The ocular picture varied from mild mucopurulent conjunctivitis to perforating corneal ulcers destroying the globe. The striking increase in the number of cases reported recently and the high percentage with ocular lesions make it important for the ophthalmologist to be aware of the ocular implications of erythema multiforme.

NOMENCLATURE

Unfortunately, the literature has been cluttered with many cumbersome names for mucosal involvement accompanying erythema multiforme of the skin. A brief survey of titles used is presented in an attempt to clarify the current nomenclature.

In 1866 Hebra [1] proposed the name "erythema exudativum multiforme" for a cutaneous disease identified by variously shaped erythematous lesions of the skin. He cited a rare variant of erythema multiforme with accompanying severe stomatitis and purulent conjunctivitis. Most dermatologic writers have subsequently adhered to the title "erythema exudativum multiforme (Hebra)."

In 1876 Fuchs [2] first stressed ocular involvement by reporting a case with pseudomembranous conjunctivitis associated with a generalized cutaneous eruption of the herpes iris type. His introduction of the term "herpes iris conjunctivae" probably accounts for the condition's remaining in relative obscurity in the ophthalmologic literature for so many years. Several case reports appeared under these two

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Presented in brief before the staff meeting of the Children's Hospital Jan. 9, 1949.

1. Hebra, F.: On Diseases of the Skin, Including the Exanthemata, translated and edited by C. H. Fagge, London, New Sydenham Society, 1866, vol. 1.

2. Fuchs, E.: Herpes Iris Conjunctivae, Klin. Monatsbl. f. Augenh. **14**:333, 1876.

captions (Kaposi,[3] Hanke,[4] Barkan[5] and Blair[6]), until in 1916 the title "ectodermosis erosiva pluriorificialis" appeared (Rendu[7]). In 1922 Stevens and Johnson[8] reported their 2 classic cases under the title "eruptive fever with stomatitis and ophthalmia." Many writers[9] have subsequently adopted some variation of the caption, such as "eruptive fever involving mucous membranes" or simply "Steven-Johnson disease." Other titles that have been used in an attempt to describe the prominent symptoms are "dermatostomatitits" (Baader[10]), "erythema multiforme pluriorificialis" (Erger[11]), "fatal bullous dermatitis" (Fitzgerald[12]) and "erythema bullosum malignans—pluriorificial type" (Costello[13]). Lastly, when involvement of the respiratory tract accompanies the eruption, the caption "mucosal respiratory syndrome" (Stanyon and Warner[14]) has been used. It is recommended that the picture be classified as erythema multiforme bullosum with mucosal involvement, or erythema multiforme bullosum. This designation,

3. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, in Vorlesungen für praktische Aerzte und Studirende, ed. 4, Vienna, Urban & Schwarzenberg, 1893.

4. Hanke, V.: Der Herpes Iris des Auges, Arch. f. Ophth. **52**:263, 1901.

5. Barkan, H.: Herpes Iris of the Conjunctiva, Arch. Ophth. **42**:236, 1913.

6. Blair, L. E.: A Case of Recurring Membranous Stomatitis Associated with Erythema Exudativum Multiforme, M. Rec. **65**:729, 1904.

7. Rendu, R.: Sur un syndrome caracterisé par l'inflammation simultanée de toutes les muqueuses externes (conjonctivale, nasale, linguale, bucco-pharnygée, anale et balano-préputiale) coexistant avec une éruption varicelliforme puis purpurique des quatres membres, Rev. gén. de clin. et de thérap. **30**:351, 1916.

8. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia: Report of Two Cases in Children, Am. J. Dis. Child. **24**:526 (Dec.) 1922.

9. (*a*) Wheeler, J. M.: Destructive Purulent Ophthalmia Accompanying an Eruptive Fever with Stomatitis, Tr. Am. Acad. Ophth. **34**:179, 1929. (*b*) Murphy, R. C., Jr.: Eruptive Fever Involving Mouth and Eyes (Stevens-Johnson Disease): Report of Case, New England J. Med. **230**:69, 1944. (*c*) Soll, S. N.: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis, Arch. Int. Med. **79**:475 (May) 1947.

10. Baader, E.: Dermatostomatitis, Arch. f. Dermat. u. Syph. **140**:261, 1925.

11. Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), Mil. Surgeon **95**:308, 1944.

12. Fitzgerald, P. J.: Fatal Bullous Dermatitis with Multiple Lesions of the Mucous Membranes, U. S. Nav. M. Bull. **47**:134, 1947.

13. Costello, M. J.: Erythema Multiforme Exudativum (Erythema Bullosum Malignans—Pluriorificial Type): Personal Observations in Willard Parker Hospital for Contagious Diseases (1932-1946), J. Invest. Dermat. **8**:127, 1947.

14. Stanyon, J. H., and Warner, W. P.: Mucosal Respiratory Syndrome, J. Canad. M. Serv. **3**:111, 1946.

originally suggested by Ageloff,[15] is inclusive of the varied symptoms and conforms to better standards of nomenclature.

CLINICAL PICTURE

The clinical picture is characterized at its onset by a nonspecific conjunctivitis and stomatitis, followed shortly by a generalized erythematous eruption of the skin. The mucous membranes of the genitalia have also been involved in approximately one fourth of the reported cases, and involvement of the mucosa of the alimentary tract and tracheobronchial tree has been recorded.[14] Typically, the oral lesions become vesicular and then break down during the first three to four days to leave large, raw areas. In about one week the cutaneous lesions undergo vesiculation, rupture and leave raised hemorrhagic crusts. At the end of two weeks the cutaneous lesions slowly begin to heal and the oral lesions to epithelize. The ocular signs will be considered in more detail.

A mild, nonspecific, bilateral catarrhal conjunctivitis characterizes the onset of ocular symptoms. In two to four days secondary bacterial infection occurs, and a copious mucopurulent or purulent discharge appears. Small vesicles frequently form on the swollen and reddened conjunctiva; these rupture and leave denuded areas. The corneal epithelium may become abraded, with resulting superficial ulceration of the cornea. An accompanying intense anterior uveitis (Ginandes,[16] Rutherford,[17] Bailey,[18] Stevens and Johnson[8]) has been recorded, and perforation of corneal ulcers, with resulting phthisis bulbi, occurred in the cases of Stevens and Johnson,[8] Wheeler,[9a] Rutherford[17] and Shaffer and Morris.[19] A pseudomembrane may form on the palpebral and bulbar conjunctiva, and when the conjunctival involvement is a severe necrotizing type a true membrane may form. Removal of this true membrane leaves a raw surface with many fine bleeding points. Reformation of the membrane occurs in twenty-four to forty-eight hours. Typically, after from three to six days in the milder cases, and from ten to fourteen days in the severer ones, the ocular picture begins to

15. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson Disease): Report of Case, New England J. Med. **223**:217, 1940.

16. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), Am. J. Dis. Child. **49**:1148 (May) 1935.

17. Rutherford, C. W.: Membranous Conjunctivitis with Loss of Eyeballs: Report of Cases, Tr. Sect. Ophth., A. M. A., p. 169, 1929.

18. Bailey, J. H.: Lesions of Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, Arch. Ophth. **6**:362 (Sept.) 1931.

19. Shaffer, B., and Morris, P.: Severe Erythema Multiforme of the Pluriorificial Type, Pediatrics **2**:30, 1948.

subside. The conjunctival epithelium, and the corneal epithelium if involved, begin to epithelize. During the healing of corneal ulcers there may be superficial, and occasionally deep, corneal vascularization, and faint nebulas to dense opacities, with severe visual loss, result. Symblepharon formation is frequent in the severer cases. Dense conjunctival adhesions obstructed the lacrimal flow in 1 case,[20] and keratoconjunctivitis sicca resulted. In this case recurrent corneal ulcers followed the keratoconjunctivitis sicca, one of which perforated with loss of the eye. Scarring and thickening of the palpebral conjunctiva frequently deforms the inner surface of the lid, and entropion of both lower lids was the result in 1 case (Stark[21]). The scarred lid sometimes resembles the cicatricial stage of trachoma.

Ocular Lesions in Erythema Multiforme with Involvement of the Mucous Membrane

		Previously Reported Series	Author's Series
Cases reviewed		162	16
Cases with ocular involvement		148	13
A. Bilateral catarrhal or purulent conjunctivitis without other ocular lesions	75		8
B. Bilateral purulent conjunctivitis with membrane formation	51		3
C. Corneal ulceration accompanying conjunctivitis*	22		3
Anterior uveitis	3		0
Corneal ulcers perforating	5		0
D. Residual ocular sequelae			
Symblepharon formation	12		1
Marked scarring of lids	8		1
Permanent corneal opacities	14		1
Keratoconjunctivitis sicca	1		0

* Cases with corneal ulcers are not classified separately under A and B because of the inadequate description of the ocular picture in many of the cases reported.

ETIOLOGY

No known etiologic factor in the syndrome of mucosal involvement with erythema multiforme has been established. Cultures of the material from cutaneous, oral, conjunctival and genital lesions in the cases reviewed and in the present series revealed only secondary invading pyogenic organisms. Cultures of the blood and of the vesicular fluid were likewise noncontributory. The possibility of a virus has been suggested, but no virus has been isolated. Jones and associates[22] found no virus inclusion bodies in conjunctival and vaginal scrapings. Their complement fixation tests and those of Soll[8c] revealed nothing signifi-

20. Richards, J. M., and Romaine, H. H.: Keratoconjunctivitis Sicca: Sequela to Purulent Erythema Exudativum Multiforme, Am. J. Ophth. **29**:1121, 1946.

21. Stark, H. H.: Membranous Conjunctivitis of Over Four Years' Duration, Am. J. Ophth. **1**:91, 1918.

22. Jones, W. Y.; Talbot, F. F., and King, W. F.: Stevens-Johnson Disease: Case Report, Am. J. Ophth. **29**:185, 1946.

cant. Soll's [22] and Koke's [23] inoculations of denuded corneal epithelium in rabbits were unsuccessful. Injection of fluid from skin and oral vesicles in animals likewise produced nothing significant in the cases reviewed and in this series. Chick and Witzberger [24] suggested that Vincent's infection associated with altered tissue sensitivity is an etiologic factor. Smears in typical cases have not shown the specific organism. In view of these, and many other, negative results, it is interesting that Gerke and Kain [25] in 1892 grew a pure culture of Vincent's organism from conjunctival lesions in a typical case. On transferral of this culture to rabbits and human subjects, he reported membranous conjunctivitis resulting in each. Unfortunately, these results have not been duplicated.

Two patients in the present series were studied in an attempt to isolate a virus. Bullous fluid and whole blood were collected during the febrile stage for each patient. Extracts of the blood and of the fluid were planted on chick embryos and inoculated into laboratory animals, without isolation of an organism. Corneal inoculation was also without results in rabbits. Serial virus neutralization tests of the blood of these patients failed to show significant neutralization or change in titer against any of the standard virus groups. Current studies on 2 additional patients are being carried out at the National Institute of Health, under the supervision of Dr. Karl Habel. The laboratory investigations on these patients will be analyzed in detail in a subsequent report.

PATHOLOGY

The pathologic picture (McCarthy [26]) is that of any nonspecific acute inflammatory process. In the skin there is an inflammatory reaction characterized by edema, congestion and hemorrhage, followed by round cell infiltration and finally by exudation of fluid splitting the cell layers, with formation of vesicles and sloughs. In the lesions of the mucous membranes a similar reaction occurs. Depending on the amount of intercellular edema, small bullae appear, which subsequently rupture. In the eye, fibrinous exudates may mesh inflammatory cells and dead epithelial cells, with the formation of pseudomembranes. These are readily removed without bleeding. In some cases a severe necrotizing reaction occurs, with sloughing of the conjunctival epithelium and

23. Koke, M. P.: Conjunctivitis in Erythema Exudativum Multiforme: Report of Three Cases, Arch. Ophth. **25**:78 (Jan.) 1941.

24. Chick, F. E., and Witzberger, C. M.: Erythema Multiforme Exudativum Accompanying Oral Vincent's Infection, Am. J. Dis. Child. **55**:573 (March) 1938.

25. Gerke, O., and Kain, E.: Ein Fall von Croup der Bindehaut der Mund- und Rachenschleimhaut, Arch. f. Augenh. **24**:305, 1892.

26. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

the subepithelial layer, which form true membranes. Removal here is more difficult, and a raw, bleeding surface is uncovered. Sections of enucleated eyes have revealed only a nonspecific inflammatory response (Ginandes,[18] Richards and Romaine [20]).

DIFFERENTIAL DIAGNOSIS

Many drugs may produce a reaction resembling typical erythema multiforme bullosum. Many investigators, including Wheeler,[24] Shaffer and Morris [19] and Folk,[27] have reported cases of typical erythema multiforme bullosum in which a definite history of drug intake was obtained. The fact that no etiologic agent has been established makes tenable the report of these cases as instances of erythema multiforme rather than primarily of a drug reaction. It would be preferable, however, when a history of an offending drug is established, that the condition be classified primarily as a drug reaction of the erythema multiforme type.

Differentiation from pemphigus of the mucous membrane may be difficult. In pemphigus, however, the condition is more chronic, the patients are usually of an older age group and a positive Nikolsky sign can sometimes be obtained.

In many of the cases reviewed the patients were admitted to contagious disease hospitals with various diagnoses. Among these were hemorrhagic measles, diphtheria, chickenpox, smallpox, impetigo and secondary syphilis. Differentiation of these diseases may at first prove difficult, but the clinical course and laboratory studies usually bear out the true diagnosis.

Other diseases which have been less commonly confused with erythema multiforme bullosum are aphthous stomatitis ("foot and mouth disease"), Vincent's infection and vitamin B deficiency.

TREATMENT

No specific therapy has been evolved. Administration of penicillin or other antibiotics to combat secondary infection, together with general supportive measures, is recommended. Care of the ocular involvement should include frequent conjunctival irrigations with bland solutions and instillation of the antibiotics to combat secondary infection. Symptomatic treatment of any complication is carried out in the routine manner, with particular attention directed to the integrity of the corneal epithelium at all times.

The antihistaminic drugs have been used and are strongly recommended, with the possibility that the condition may be related to histamine toxicity. Although favorably reported on by several investigators

27. Folk, M. R.: Erythema Exudativum Multiforme, Am. J. Ophth. **31**:621, 1948.

and employed with apparently good results in 4 cases of my series, conclusive evidence for the efficacy of these drugs is wanting. Wheeler [79] recommended that early canthotomy be considered in cases in which severe swelling of the lids prevents adequate irrigation of the cul-de-sacs.

COMMENT

An increasingly large number of cases of mucosal involvement accompanying erythema multiforme has recently appeared in the literature.[28] Proper recognition and diagnosis are probably responsible

28. (*a*) Murphy.[9b] (*b*) Soll.[9c] (*c*) Baader.[10] (*d*) Erger.[11] (*e*) Fitzgerald.[12] (*f*) Costello.[13] (*g*) Stanyon and Warner.[14] (*h*) Ageloff.[15] (*i*) Ginandes.[16] (*j*) Rutherford.[17] (*k*) Bailey.[18] (*l*) Shaffer and Morris.[19] (*m*) Richards and Romaine.[20] (*n*) Stark.[21] (*o*) Jones and others.[22] (*p*) Koke.[23] (*q*) Chick and Witzberger.[24] (*r*) Gerke and Kain.[25] (*s*) Association of Pneumonia with Erythema Multiforme Exudativum, Commission on Acute Respiratory Disease, Arch. Int. Med. **78**:687 (Dec.) 1946. (*t*) Dugan, J.: Erythema Multiforme Bullosum (Stevens-Johnson Disease), Clin. Proc. Child. Hosp. **2**:298, 1946. (*u*) Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children, with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **12**:151, 1938. (*v*) Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra)—Bullous Type: Cases Seen in Contagious Disease Hospital, ibid. **27**:465, 1945. (*w*) Givner, I., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762, 1941. (*x*) Goldfarb, A. A.: Case of Stevens-Johnson Disease (Erythema Multiforme Bullosa), Treated with Penicillin, J. Pediat. **28**:579, 1946. (*y*) Grossman, E. E.: Conjunctivitis Associated with Erythema Multiforme Bullosa, Am. J. Ophth. **29**:1146, 1946. (*z*) Keil, H.: Erythema Multiforme Exudativum (Hebra): Clinical Entity Associated with Systemic Features, Ann. Int. Med. **14**:449, 1940. (*a'*) Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611, 1945. (*b'*) Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of Type Ectodermis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One Case, Arch. Dermat. & Syph. **49**:47 (Jan.) 1944. (*c'*) Levy, A. T.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Mouth (Stevens-Johnson Disease), J. Am. Dent. A. **30**:287, 1943. (*d'*) Meisenhelder, E.: Stevens-Johnson Disease: Report of Case, Arch. Ophth. **36**:631 (Nov.) 1946. (*e'*) Robinson, H. C.: Erythema Multiforme: Report of Case of Severe Erythema Multiforme with Involvement of Mucous Membranes Treated with Penicillin, Arch. Dermat. & Syph. **52**:91 (Aug.) 1945. (*f'*) Rosenberg, L., and Rosenberg, J.: Erythema Exudativum Multiforme (Hebra) with Conjunctivitis and Stomatitis, ibid. **41**:1066 (June) 1940. (*g'*) Stevenson, J.: Erythema Multiforme, with Unusual Manifestations, J. Oklahoma M. A. **39**:443, 1946. (*h'*) Umiker, W., and Crofoot, M.: Stevens-Johnson's Disease, U. S. Nav. M. Bull. **46**:1466, 1946. (*i'*) Weisberg, A., and Rosen, E.: Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **53**:99 (Feb.) 1946. (*j'*) Wentz, H. S., and Seiple, H. H.: Stevens-Johnson Syndrome: Variation of Erythema Multiforme Exudativum (Hebra): Report of Two Cases, Ann. Int.

for the report of this large number; however, an increase in prevalence of the condition is suspected.

Six fatal cases have previously been recorded, death usually occurring when bronchopneumonia complicated the clinical picture. Death occurred in 2 cases of my series. In these cases the condition was considered primarily as a drug reaction with the picture of erythema multiforme bullosum. A history of phenobarbital ingestion in 1 case and of dexedrine[9] (D-amphetamine sulfate) intake in the other was obtained.

Disastrous ocular sequelae have been recorded. Wheeler's [8a] patient showed bilateral corneal ulcers which perforated, with total blindness resulting in one eye and reduction of vision to light perception in the other. In Rutherford's [17] case, enucleation of both eyes was done when corneal ulcers perforated. In the case of Richards and Romaine,[20] keratoconjunctivitis sicca resulted from obstruction of lacrimal flow by adhesions of the superior cul-de-sac. Recurrent corneal ulcers appeared after the acute stage of the disease subsided, and one of these ulcers perforated, to destroy the eye. Ginandes [16] reported a case of purulent enophthalmitis accompanying an annular corneal abscess, which necessitated enucleation of one eye. In 2 cases of Bailey [18] and in 1 case of Stevens and Johnson [8] almost complete blindness resulted from the corneal and intraocular involvement. In Shaffer's [19] case a reaction to trimethadione resulted in blindness in both eyes, with corneal perforation occurring in one eye.

Several investigators have adopted some variation of the caption "eruptive fever with involvement of mucous membranes." This title, although I have used it previously,[21r] is misleading, as fever is frequently not a prominent symptom and no association with erythema multiforme is suggested. One fifth of the reviewed cases were reported under the title "Stevens-Johnson disease." This adoption of proper names is only to be criticized, as no descriptive value is obtained from the title and no information is rendered the investigator who is attempting

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Med. **26**:277, 1947. (*k'*) Nellen, M.: Stevens-Johnson Syndrome, Lancet **1**:326, 1947. (*l'*) Murray, J. O.: Stevens-Johnson Syndrome: Report of Two Cases, ibid. **1**:328, 1947. (*m'*) Lindsay, W. K.: Mucosal Respiratory (Stevens-Johnson) Syndrome, Canad. M. A. J. **56**:527, 1947. (*n'*) Schremperlen, C. B.: Benadryl in Treatment of Mucosal Respiratory Syndrome, ibid. **56**:73, 1947. (*o'*) Wright, D. O.; Gold, E. M., and Jennings, G.: Stevens-Johnson Syndrome: Report of Nine Patients Treated with Sulfonamide Drugs or Penicillin, Arch. Int. Med. **79**:510 (May) 1947. (*p'*) Haddad, N. N.: Muco-Cutaneous Fever, J. Canad. M. Serv. **2**:657, 1945. (*q'*) Hogan, M. J.: Conjunctivitis with Membrane Formation, Am. J. Ophth. **30**:1495, 1947. (*r'*) Nathan, A.; Cameron, P. J., and Zelson, C.: Erythema Multiforme Bullosa (Stevens-Johnson Type), New York State J. Med. **48**:1611, 1948. (*s'*) Hoffman, I. L., and Stone, T. E.: Report of Case of Stevens-Johnson Disease, Mil. Surgeon **102**:494, 1948. (*t'*) Patz, A.: An Eruptive Fever Involving Skin and Mucous Membranes, New England J. Med. **236**:697, 1947.

to identify his cases. The designation "erythema multiforme bullosum with mucosal involvement" is inclusive of all symptoms and conforms to the principles of better nomenclature.

Duke-Elder [29] classified the types of the conjunctival involvement accompanying erythema multiforme as catarrhal, purulent and pseudomembranous. He cited the pseudomembranous type as occurring most frequently; however, in the cases reviewed and in this series, purulent conjunctivitis was found most commonly.

In view of the increased prevalence of the condition, it is suggested that the ophthalmologist question his patient with atypical conjunctivitis or unusual conjunctival and corneal scarring for the presence of accompanying or preceding stomatitis and cutaneous eruptions.

Four typical cases of ocular involvement in erythema multiforme are presented.

REPORTED CASES

Case 1.—P. D.,[30] boy aged 8 years, was admitted with burning, watery eyes, sore throat and painful urination. Examination revealed that he was an acutely ill child, with a generalized maculopapular and vesicular eruption of the skin. The palpebral and bulbar conjunctivas were swollen and acutely inflamed, and small vesicles were present on the palpebral conjunctivas. The corneas were clear on his admission, and the eyes were otherwise normal. Many large vesicles were present on the lips, the oral mucosa and the glans penis.

Laboratory studies revealed nothing remarkable except for a lowered thrombocyte count.

During the first three days the eyes were irrigated frequently with boric acid and penicillin solution, and general supportive care was given, including intravenous injection of fluids, blood transfusions and intramuscular injection of penicillin.

The conjunctivitis became purulent, and pseudomembranes formed, which were easily removed without bleeding. The vesicles on the conjunctiva of the upper eyelids ruptured, leaving raw, denuded areas. The conjunctivitis persisted, and on the tenth day in the hospital superficial central corneal ulcers, with surrounding corneal infiltrates, were detected in each eye. Instillation of atropine was started, and the local use of penicillin was increased to once every two hours. The ulcers healed in ten days, and by the fourteenth day the conjunctivitis had begun to subside. The raw areas on the upper lids gradually healed, with thickening and roughening of the inner surface. The corneal infiltration cleared slightly; the central opacities, however remained moderately dense. Superficial vascularization spread over the cornea from the limbus in each eye. The patient was discharged after eleven weeks with vision of 20/70 in each eye. At no time was there any intraocular involvement.

Examination nine months after discharge revealed a healthy youngster with vision of 20/40 in the right eye and 20/30 in the left eye. The central corneal

29. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

30. This case has previously been reported.[28e] The patient's course over a three year period, together with the original ocular picture, is presented.

opacities had cleared somewhat (fig. 1); however, the vascularization had not changed. The upper lids were scarred on the inner surface and slightly thickened. Intraocular examination revealed nothing abnormal.

Three years after onset of the disease, vision with correction was 20/40 in each eye. The corneal ulcers had faded slightly, but residual superficial vascularization was visible. The scarring of the upper lids was still evident. A small area of peripheral chorioretinitis, believed to be unrelated to the erythema multiforme, was detected in the left eye.

CASE 2.—N. A., a white soldier aged 20, was admitted to the hospital on Nov. 6, 1946 with a history of sore mouth, fever and a cutaneous rash of two days' duration. Examination revealed a temperature of 103 F., severe bullous stomatitis, balanitis, purulent conjunctivitis and an erythematous, maculopapular eruption of the skin. Laboratory studies revealed nothing significant except for Staphylococcus aureus in cultures obtained from the oral lesions and the conjunctiva. The cutaneous lesions became vesicular and ruptured, as did the oral bullae. The severity of the oral lesions necessitated parenteral feedings for forty-eight hours. After two weeks the cutaneous, oral and genital lesions gradually began to clear

Fig. 1 (case 1).—Central corneal lesion nine months after the patient's discharge.

and the conjunctivitis to subside. At no time was there corneal or intraocular involvement.

After a normal interim of seven months, the patient was readmitted with an erythematous, maculopapular eruption, which was followed by bullous stomatitis, balanitis and catarrhal conjunctivitis in both eyes. Treatment was started with diphenhydramine hydrochloride, 200 mg. daily, shortly after his admission. The cutaneous lesions cleared without undergoing vesiculation, and the conjunctivitis subsided rapidly. The oral bullae, however, ruptured, to leave large raw, denuded areas (fig. 2). On about the fifth day in the hospital the oral lesions began to epithelize, and the mouth was completely healed at the end of the second week. Laboratory studies, including blood counts, thrombocyte counts, urinalysis and cultures of conjunctival and oral secretions and of the blood, revealed nothing significant. Agglutination tests all gave negative results. Repeated dark field examinations and smears of material from the oral and penile lesions showed no evidence of Vincent's infection or of syphilis.

CASE 3.—C. A., a boy aged 13, was admitted to the ophthalmologic service in September 1947, having been shot in the left eye with a BB shot. The pellet was removed from its subconjunctival position in the lower cul-de-sac. The inferior

nasal retinal quadrant was raised, and several small peripheral hemorrhages were noted. The patient was restless and was placed under treatment with phenobarbital (½ grain [8 mg.]) three times a day. On the eighth hospital day the patient became acutely ill. The temperature spiked to 102 F, and severe conjunctivitis, intense stomatitis and a generalized maculopapular rash appeared. The conjunctivitis became purulent, and the oral and cutaneous lesions became vesiculated to form large bullae. After about five days the conjunctivitis began to subside; however, a sticky, purulent exudate persisted. The oral and cutaneous vesicles had ruptured and began to epithelize. The cutaneous lesions healed after ten days. No corneal or intraocular involvement was noted at any time except for the initial traumatic separation of the retina, which was sealed back without event. Leukocytosis, with a count of 15,300 per cubic millimeter, and a shift to the left, cultures

Fig. 2 (case 2).—Large bulla on the buccal mucosa during recurrence of the disease.

of Staph. aureus obtained from conjunctival and oral lesions were the only significant laboratory findings.

Case 4.—M. O., a Negro woman aged 24, gave a history of having taken d-amphetamine sulfate, 5 mg. three times daily, for two months prior to admission. Two days before admission she became acutely ill and noted a generalized cutaneous eruption, sore mouth and swelling about the eyes.

Physical examination showed a temperature of 105 F. and a generalized maculopapular eruption on the skin, with several large ruptured or unruptured vesicles on the back, shoulders and face (fig. 3*B*). The lids were greatly swollen and presented large confluent bullae on the upper and lower lids of both eyes. Gentle manipulation to open the eyes resulted in breaking these bullae and leaving raw areas (fig. 3*A*). The corneas and bulbar conjunctivas were covered with thin, grayish white pseudomembranes, which wiped away readily without bleeding. The

corneas showed no staining, and intraocular examination revealed nothing abnormal. Large bullae were present in the mouth and vagina. Examination of the chest revealed bronchopneumonia, with the physical signs more pronounced at the base of the left lung.

The patient was placed under treatment with intramuscular injections of penicillin, administration of tripelennamine (pyribenzamine®) hydrochloride, 100 mg. every four hours, instillation of penicillin drops in the eyes hourly and general supportive care. She became progressively worse and died on the fourth day in the hospital. Permission for pathologic examination was not obtained. The results of

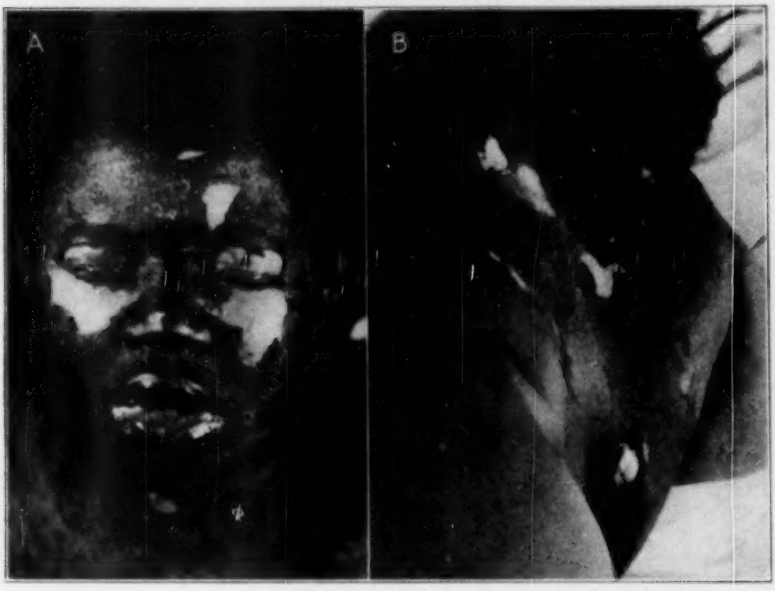

Fig. 3 (case 4).—*A*, denuded areas where vesicles ruptured on the manipulated lids, encrusted lips and maculopapular lesions on trunk; *B*, intact and freshly ruptured vesicles on the back.

laboratory studies were not remarkable, and cultures of material from the mouth, eyes and vagina yielded only a growth of Staph. aureus.

SUMMARY

When involvement of the mucous membranes accompanies erythema multiforme bullosum, the picture is characterized by purulent or membranous conjunctivitis, stomatitis and an erythematous, vesicular eruption of the skin. The mucous membranes of the genitalia and the respiratory tract are occasionally involved.

A review of 162 previously reported cases with lesions of the mucous membranes revealed ocular involvement in 148. Ocular lesions were found in 13 of my series of 16 cases. Purulent or membranous conjunctivitis or a combination of the two was the commonest ocular sign. Corneal ulceration occurred in 14 per cent of patients with ocular lesions. Complications and sequelae of ocular involvement included perforation of corneal ulcers with loss of the globe, symblepharon formation, scarring of the lids, corneal opacities and keratoconjunctivitis sicca.

The varied titles that have been adopted are surveyed, with the hope that some clarification of nomenclature can be accomplished. The designation of "mucosal involvement in erythema multiforme bullosum" is recommended.

NOTE.—Aureomycin hydrochloride has recently been used systemically with good results in 3 typical cases. An antiviral action may have occurred in these cases; however, prevention of secondary bacterial infection is thought to explain the therapeutic effect.

OCULAR FATIGUE

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RESPONSIBLE persons in factories, offices and schools are frequently confronted with the question whether existing illumination is inadequate and is causing ocular fatigue. At the present time there are no methods of determining objectively satisfactory illumination.

PRESENT STUDY

The purpose of this investigation was to determine whether there were any physiologic tests which could be used to demonstrate the ocular fatigue which occurs during the working day, and which could be used to differentiate good and poor illumination.

The problem was approached by testing various ocular functions at the (*a*) start of, (*b*) during and (*c*) at the end of the working day. The various functions tested under numerous conditions were: (1) acuity for far; (2) acuity for near; (3) speed of accommodation from far to near; (4) changes in heterophoria; (5) loss of ability to converge, as measured by the ability to overcome diplopia against increasing diopters of prism, base out; (6) near point of accommodation, and (7) ability to sustain accommodation.

The 8 subjects in these experiments were persons doing fairly close work under artificial illumination of 5 foot candles, conditions such as one might find in any business office. Six of the subjects were women and 2 were men, and their ages varied from 21 to 54. Three of the women were librarians whose work consisted in filing cards and books; 2 were clerks operating complicated business machines, and 1 was a stenographer. One of the men was a mail clerk whose work consisted of sorting letters; the other a research worker who read during the day. The working day was from 9 a. m. to 5 p. m. with one hour off for lunch. Subjects were tested before starting to work, at times before the lunch hour and just before stopping work.

Illumination was measured using the Macbeth illuminometer for illuminations below 5 foot candles and a General Electric photoelectric exposure meter for illuminations above 5 foot candles.

From the Laboratory of Industrial Physiology, Graduate School of Business Administration, Harvard University.

Acuity for far was tested for each and for both eyes with the standard Snellen chart at 20 feet (6 meters) and an illumination of 20 foot candles. There was no decrease in the ability to read the chart after a working day as measured by the number of errors. In order to make the test more sensitive, the time during which the subject was permitted to view each letter was limited to one second and the total number of letters of each size not read in the required time, as well as the number of errors, was counted. There was no increase in the number of letters not read in the required time, or in the number of errors, after a working day. It was thought possible that losses in acuity might be demonstrable if sufficiently low illuminations were used during the test. Therefore the tests were conducted at illuminations of 1, 0.1, 0.05, 0.02, 0.01 and 0.002 foot candles. The total time required for the subject to read the entire line (i. e., 20/20; 20/30, etc.) was measured, as well as the number of errors. Under these conditions, there was no increase in the number of errors and no significant increase in the time required, but the subject felt that he was exerting more effort. Then the illumination was gradually increased until the subject was just able to read the 20/20 line, and the illumination was measured. Repetition of this test after the day's work revealed no loss of acuity for far during the working day as tested by this method. None of the methods used showed any loss of acuity for far after a working day.

Acuity for near was tested using the American Optical Company's reading card, the American Optical Company's card for illiterates and the Guibor near point card for illiterates at 14 inches (35.5 cm.) with an illumination of 5 foot candles. There was no loss in the ability to read the chart after a working day as measured by the number of errors. Then, in an attempt to make the test more sensitive, the illumination was decreased under various conditions. 1. After five minutes' adaptation, using the Guibor chart for illiterates (figure E pointing in eight directions, with the total letter subtending 5 minutes of angle), at a distance of 14 inches, the subject attempted to read the 14/14 line as the illumination was increased. When the subject could just read the 14/14 line (i. e., ten consecutive letters correctly), the illumination was measured. The 14/17.5 and 14/12 lines were also attempted at the same illumination, and the number of errors was counted. After a day's work, the illumination was set at the same point and the subject attempted to read ten letters of each line. There was no increase in the number of errors after the day's work.

2. After a ten minute period of adaptation, using the American Optical Company's chart for illiterates (figure E in four directions),

with the illumination set at 1, 0.1 and 0.05 foot candle on different occasions, the subject attempted to read ten letters of the 14/14 line at 14 inches. The number of errors was counted, and the total time required to read ten letters was measured. This test was repeated after a day's work, under the same illumination. There was no increase in the number of errors after a day's work and no consistent increase in the length of time required. 3. After five minutes' adaptation, with the American Optical Company's chart for illiterates at 14 inches, the illumination was gradually increased until the subject could just read the letters of the 14/14 line correctly. This illumination was measured, and the subject continued to read this line until it became so blurred that he could not read it. The total number of letters and the number of errors were counted. After a day's work, under the same illumination, when the subject again attempted to read this line, there was no decrease in the number of letters read before blurring and no increase in the number of errors. 4. The illumination was increased until the subject could just read ten letters of the 14/14 line correctly (after five minutes' adaptation), and the illumination was measured. After the day's work, the illumination was set at the same point, and the subject again attempted to read the same line, which he was able to do with no increase in errors. 5. Using the American Optical Company's chart for illiterates, with the illumination set at 5 foot candles, the subject attempted to read ten consecutive letters of the 14/14 line in ten seconds. The number of errors, as well as the number of letters not read, was counted. After a day's work the experiment was repeated under the same conditions, with no increase in the number of errors or in the number of letters not read. There was no evidence in any of these tests of a loss of acuity for near as a result of a day's work.

Acuity for near was also tested using the Landolt circles with one, two and three breaks. The circles were so constructed that the total figure subtended an angle of 5 minutes at distances of 11, 12, 13, 14, 15 and 16 inches (28, 30, 33, 35.5, 38 and 41 cm.) and the width of the circles and the width of the break subtended an angle of 1 minute at the same distances. These figures were constructed in black on white, one hundred times the size designated and photographically reduced, then printed on glossy paper. The figures were read at 14 inches, with an illumination of 2.0 foot candles, against a white background, the figures being placed in any one of the four (horizontal or vertical) positions. The results with this test were much more uniform and reproducible than those obtained with any of the previous tests for acuity. There was no evidence with this test that any loss of acuity for near occurred during the working day.

The speed of accommodation from far to near was next tested. It was felt that speed of accommodation from far to near, requiring contraction of the circular fibers of the ciliary muscle, would be much more likely to show effects of fatigue after near work than speed of accommodation from near to far. With the method used, the subject looked at the large E of the Snellen chart at 20 feet with an illumination of 20 foot candles. Then a —4.0 △ lens was dropped in front of the subject's eye; this placed a virtual erect, smaller image of the large E 25 cm. in front of the eye, and the eye accommodated for it. An electric timing clock was attached to the apparatus, which was started when the lens dropped in front of the eye and stopped when the subject released a switch at the point at which the near image became clear. Ten consecutive tests were made on each eye before and after a day's work. There was no evidence of fatigue as shown by lengthening of the speed of accommodation from far to near. In fact, the time in the evening was consistently shorter, suggesting possibly a "warming-up" effect, such as a sprinter gets with some practice.

Heterophoria was tested for before and after a day's work, using an American Optical Company eiconometer. There were no consistent changes, a result which is to be expected if one considers the position that the eyes assume under such conditions as the result of reflex tone from all sources less the visual fixation reflex.

Fatigue of the two internal rectus muscles [1] after a day's work was tested by the ability of these muscles to prevent diplopia against prisms of increasing dioptric strengths base out as tested in the morning and in the evening. There was no consistent or significant loss of this ability after a day's work.

The near point of accommodation was tested before, during and after a day's work. The test object used was a modification of the Ferree and Rand "li" test object, which consisted of the letters *li* printed in black 8 point type [2] on a white card, the task being to resolve and hold clear the break between the dot and its stem in the letter *i* (breadth of the break, 0.62 mm.). In the modification used, there were two sets of *li;* one set was placed just adjacent, and 5 mm. posterior, to the other set.

1. Ferree, C. E., and Rand, G.: Effect of Variations in Intensity of Illumination on Acuity, Speed of Discrimination, Speed of Accommodation and Other Important Eye Functions, Tr. Am. Ophth. Soc. **19**:259-297, 1921.

2. Ferree, C. E.: Tests for the Efficiency of the Eye Under Different Systems of Illumination and a Preliminary Study of the Causes of Discomfort, Tr. Illum. Engin. Soc. **8**:40-60, 1913; Investigation of the Reliability of the "Li" Test in Discussion on Luckiesh, M.; Cobb, P. W., and Moss, F. K.: ibid. **22**:52-75, 1927.

In this arrangement the subject fixated on the anterior *li* but was able to perceive the posterior *li* as well. With this separation in depth, when the observer fixated on the anterior *li*, situated at points beyond his near point of accommodation, both *li's* appeared sharp, for both were within his depth of focus. However, as the nearer *li* was brought closer to the observer's eye than his near point of accommodation, it became fuzzy and contrasted sharply with the more distant *li*, which was still beyond his near point and was clear. All the subjects stated that this test object enabled them to tell more accurately the point at which the anterior *li* became fuzzy as it came inside the near point.

In testing the near point of accommodation, the foregoing test object was mounted on an apparatus which enabled the subject to draw it gradually closer to his eye as he fixated on the closer *li*. The point at which the anterior *li* was first perceived to be fuzzy was considered his near point, and its distance from the anterior surface of the cornea was measured. The subject then moved the test object away from his eye until the anterior *li* again appeared clear; this point was designated as his clear point, and the distance from the anterior surface of the cornea was measured.

The near point of accommodation and the clear point were determined before work, after one to two hours of work and at the end of the working day. Both the near point of accommodation and the clear point were found to proceed after one to two hours of work, and then to have receded at the end of the working day. For most subjects, as tested by this method, the near point at the end of a day's work was farther from the observer than it had been before starting the day's work. However, for some observers, especially the younger ones, it appeared that after the initial procession, the near point did not recede to its position in the morning. Of the observers for whom the clear point had receded beyond the clear point of the morning, if the object was placed at the morning (closer) clear point and the subject was asked to attempt to see it clearly, the majority stated that they were able to see it clearly. However, if the subject was merely asked to look at the test object at the morning clear point and then positive lenses of increasing power were placed in front of the eye, all observers stated that they needed some positive lens ($+0.25$ to $+0.37$ D.) to see the anterior *li* clearly.

The near point of accommodation was also tested, at two hour intervals in a subject who worked a ten hour day, in sorting letters under poor illumination. The illumination was 10 foot candles with some glare source. This subject showed procession at two hours and

the recession at four hours, with a similar reaction after lunch, though the procession was not as much and the recession was farther. He was also tested after working with a more definite glare source, which gave an illumination of 20 to 40 foot candles at the point where he worked. The results were similar to those already described, but of greater magnitude. He was then tested after working under indirect illumination of 20 to 30 foot candles, and his procession was found to be delayed and his recession much slower and of smaller amount. The subject felt that this illumination was much superior, that his work was easier and that he tired less. It appeared that with better illumination the near point proceeded more slowly and receded more slowly and to a smaller amount during the working day. More subjects working under equally difficult conditions should be tested in this way before any definite conclusions can be reached.

The ability to sustain accommodation was tested with the same test object used in determining the near point of accommodation. The observers looked at the test object (anterior *li*) for three minutes, and the total time that the anterior *li* appeared blurred was measured and compared with the total time observed (i. e., forty seconds of blurring out of one hundred and eighty seconds of observation gives a ratio of 40:180).

When the anterior *li* was placed at the point at which it was just clear in the morning and was observed for three minutes, the time during which it was blurred being measured, and the process repeated after the day's work, at the point at which it was then just clear, there was no significant increase in the ratio of "time blurred" to "time clear."

If the test object was observed at the morning clear point, the ratio of the time during which it was blurred to the total time of observation being obtained, and then in the afternoon placed at the same point and sufficient positive lens given to enable the observer to see it clearly, most observers required some positive lens (+ 0.25 to + 0.37 D.), but time blurred to time clear was decreased slightly.

When the subject's clear point was determined before work, and the test object was then placed a greater distance away (the distance greater than the subject's previously determined amount of recession of the near point during the day's work, 1, 5 and 8 cm.) and time blurred to total time measured before and at the end of a day's work, there was a decrease in the ability to sustain good acuity, as shown by increased time blurred to total time for most subjects. This method was felt to be more satisfactory than that used by Ferree and Rand,[3]

3. Ferree, C. E., and Rand, G.: Power of the Eye to Sustain Clear and Comfortable Seeing with Different Illuminants, Am. J. Ophth. **1**:257-259, 1918.

who used (*a*) the maximal distance at which test objects could be seen clearly in the momentary judgment and (*b*) a distance less than this (i. e., 10 cm. less). All subjects stated that they were better able to tell when the test object became blurred at the distance just beyond their near point. Among young subjects there were some who had no time during which the object was blurred, either before or after the work day. There were also subjects who did not have an increase in time blurred to total time after a day's work. There appeared to be a greater tendency to show an increased time blurred to total time after a day's work with increasing age. This decrease in the ability to sustain accommodation after a day's work is believed to be due to fatigue at some point in the neuromuscular mechanism concerned with sustaining clear vision.

CONCLUSION

There does not appear to be any loss of acuity for either near or far, decrease in speed of accommodation or loss of strength of the extraocular muscles as a result of fatigue due to a working day. Of the various functions of the eye tested, only a slight recession of the near point of accommodation and a slight decrease in the ability to sustain accommodation were results which could be interpreted as being due to fatigue, and these did not occur in all subjects. It is felt that these decreases in ability noted are the result of fatigue at some point of the neuromuscular mechanisms concerned with clear seeing, most probably in the ciliary muscle. However, measurable amounts are extremely minute, and they can be demonstrated only when the eye is forced to perform its maximum accommodative effort. Within the usual ranges in which the eyes are used, there is no demonstrable decrease in ability as a result of a day's work, and what is usually called "ocular fatigue" is not the result of fatigue of the various functions. "Ocular fatigue" is probably a form of professional cramp, a focal cerebral fatigue, for if the person who complains of it attempts to perform a completely different visual task he is able to do so without difficulty. "Ocular fatigue" is similar to writer's cramp, another form of occupational neurosis, in which the patient is unable to use the hand to write because of cramping, though the hand is normal for all motor actions except that one. The person with writer's cramp may be unable to write, though still able to use his hands skilfully in playing the piano. Optimum illumination probably delays the onset of "ocular fatigue" by requiring less fixed concentration, and consequently making the mental task less difficult. Because the optimum illumination within the wide range of adequate illumination cannot be determined by objective tests of ocular function, it must be

determined subjectively by obtaining the observer's preferences in performing a particular task. Although from 1 to 10 foot candles of illumination appears to be all the light required for accurate seeing or reading, work simultaneously performed in the Laboratory of Industrial Physiology [4] by the methods described here indicates that the optimum illumination for reading, evenly distributed, of good quality, without glare source, is in the neighborhood of 20 foot candles at the working surface.

4. Holway, A. H., and Jameson, D.: Good Lighting for People at Work in Reading Rooms and Offices, Monograph Graduate School of Business Administration, Cambridge, Mass., Harvard University, June 30, 1947.

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HEMANGIOBLASTOMA OF THE RETINA (VON HIPPEL–LINDAU DISEASE)

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(Continued from page 65)

PATHOANATOMIC OBSERVATIONS

Collins [8] was the first to report pathologic observations on the disease; the previous observations had been solely ophthalmoscopic, the authors depicting the characteristic features—the enormous dilatation, the tortuosity and change in color of the vessels, and even the subsequent exudative changes—but failing to visualize the true nature of the process, the tumor formation within the retina, and concluding that the visible nodule with the two feeding vessels represented an aneurysm. Clinically, the aneurysmal nature of the nodule was questioned by the circumstance that pressure on the bulbus elicited pulsation of the vessels but that neither pulsation nor bleeding of the nodule accompanied the pressure. According to von Hippel, this lack of pulsation is evidence against the aneurysmal connection between artery and vein, and the possibility that the pulsation is concealed by the coagulation products present seems to lack factual confirmation. Other authors, such as Jacoby, emphasized that the walls of aneurysms are not necessarily thin and that coagulation does not occur in aneurysms; the door, therefore, was left open for the theory of the possible aneurysmal nature of the retinal tumor.

Collins' study, based on 3 eyes (one eye of the brother, aged 20, and both eyes of the sister, aged 26) is the very first anatomic observation which proved the true nature of the disease and was, unfortunately, overlooked not only in the early, but often even in the later, German and English literature. A host of studies begin, erroneously, with the observations of von Hippel only.

The first eye studied was the left eye of the brother, whose right eye was similarly affected, and gave the material for Wood's presentation and description. The retina was detached from the disk to the ora serrata, with a broad area of adhesion of the lower part of the inner half to the choroid at the equator. There were cholesterol crystals in the subretinal fluid, as well as granular pigment substance. Enormously dilated retinal vessels passed to the detached part of the retina; the

walls of the vessel were greatly distended; great difficulty existed in differentiation of arteries and veins. The detached part of the retina showed numerous hemorrhages; in the nondetached part the vessels were not dilated; besides numerous small dots, a large patch was visible beneath the retinal vessels. In the retinal part adherent to the choroid, the presence of a close plexus of vessels, a capillary nevus, was established.

Both the eyes of the sister, who was blind for fourteen years, showed opaque, staphylomatous corneas and discolored scleras; in the right eye a projection the size of a blackberry occupied the outer canthus. The anteroposterior axis of the right eye was 35 mm., and there was an extreme staphyloma in front of the attachments of the muscles. A large cuplike formation of bone was visible at the inner surface of the well preserved choroid; the lens, iris, ciliary body and retina were not distinguishable. In the anterior half of the globe were numerous branchings of small capillary vessels; the walls consisted mostly of a single layer of cells. Red blood corpuscles filled some of the vessels, and appeared in the tissue between the vessels. In the spaces between the vessels were cells with large nuclei, the protoplasm being delineated by a delicate network of fibers, all of them apparently originating in the nucleus. On the inner surface, toward the internal space of the eye, a tissue of variable thickness, composed of laminated spindle-shaped cells, was seen.

The left eye of the same patient measured 36.5 mm. anteroposteriorly, with a large mass of grayish tissue in the anterior part; the iris, lens, ciliary body and retina were not recognizable. The deep layers of the cornea were invaded by the tumor, which was composed of thin-walled capillary vessels, similar in structure to the tumor in the other eye. The plexus of capillaries not only invaded the cornea but formed a mass in front of the globe. Bone formation in the choroid was noted, with some vascular growth, similar to the growth in the anterior segment of the same eye. The mass situated in the cavity within the globe consisted of a network of fibrin with red and white blood elements. The tumor was bounded, except anteriorly, by dense fibrous tissue.

The three specimens had in common a growth composed of a plexus of thin-walled capillary vessels arising in the retina, some of the main vessels of which were enormously dilated and thickened. In places the growth showed cyst formation. In the spaces between the capillary vessels were cells with large nuclei, and the cytoplasm appeared to be mapped out in a honeycomb formation, similar to the cells of cerebellar angioblastoma. In all 3 cases new retinal growths were present, invading and causing absorption of the surrounding tissues (lens and iris) with encroachment on the cornea.

The second pathologic report was made by Czermak in the case in which Goldzieher gave a brilliant description of the ophthalmoscopic findings and designated the process as degeneratio fibromatosa interstitialis retinae.

Czermak observed in the right eye glial degeneration and cystic cavities in the retina and an organized and vascularized connective tissue layer with cystic cavities between the retina and the choroid, the cysts possibly being filled with cholesterol. The larger of the cavities were filled with proliferating pigment cells and unpigmented epithelial, giant and foam cells, derivatives of the pigment epithelium. The choroid was thinned out and partly infiltrated. The rods and cones and the nerve fiber layers were missing; strong proliferation of glial elements were evident. The nodules showed large arteries entering into and large veins emerging from them, with a dense network of capillaries within. The large number of convoluted blood vessels and extensive hemorrhages were responsible for the thickening of the retina. Two forms of nodules were differentiated: one with loops of vessels and hardly distinguishable remnants of preexistent retinal tissue, sharply outlined, dense in consistency and compressing the adjacent glia; and a second, of loose consistency, less sharply outlined than the first variety and with large amounts of glia between the loops. Vessels were arranged like a net or tree, with thickened adventitia, the glial proliferation being of reactive type. The loose nodules were representative of the more recent stage; the dense ones, of the older stage. The vessels not only were dilated and thickened but showed occasional infiltration of their walls. The left eye of the same patient showed the changes to a lesser degree, with preservation of the granular layers of the retina and thickening of the retina at the site of the nodule to five times the normal.

In his anatomic study, von Hippel [48] referred only to the observations of Czermak, and did not mention those of Collins. In the case of von Hippel the mass was in the lower temporal part with an area of ossification of the choroid at the posterior pole reaching the equator. In the posterior temporal part of the choroid the blood vessels were of enormous caliber, recalling the picture of cavernous angioma. The enormously dilated arteries and veins were hard to differentiate clinically. The muscular layer of the artery was distinct only adjacent to the disk; both arteries and veins showed enormous thickening of their adventitia, and arteritic and endophlebitic lumens alternated with normal ones. The cross section often revealed a picture reminiscent of thrombosis, alternating with entirely free lumens or others in which only isolated cells or delicate amorphous material was enclosed. The orientation

48. von Hippel, E.: Die anatomischen Grundlagen der von mir beschriebenen sehr seltenen Erkrankungen der Netzhaut, Arch. f. Ophth. **79**:350, 1911.

was aggravated through the extreme tortuosity of vessels, with the result that in some slides numerous cross sections of the same vessel were simultaneously shown. Nevertheless, the large artery could be followed to its termination in the spaces of the choroidal angioma; similarly, the vein, and direct communication between artery and vein, were undoubtedly demonstrated. In the tumorous portion of the retina the normal constituents were replaced by convoluted vessels embedded in glia, with extensive proliferation in some parts. The vessels were mostly of capillary type, the walls being only infrequently pronounced. With the first type the vessels, in cross section, were so closely packed that only a few glia cells were to be seen between them; with the second there was rich intermediate tissue. Parts of the retinal tumor were highly stained, owing to the presence of large protoplasmic cells and large nuclei; others showed small, degenerated nuclei only. Their possible derivation from glia cells could not be definitely proved. Parts of the tumor with rich glia and empty capillaries appeared dark and dense. Larger and smaller cavities, filled with fibrin, and retinal-suprachoroidal hemorrhages were noted. The smaller nodules were in the nerve fiber, the ganglion or the inner plexiform layer, the larger ones reaching or penetrating the internal limiting membrane. The parts of the retina adjacent to the tumor were characterized by glial proliferation and by cyst formation, enclosing coagulated material. Adjacent to the disk, loose nodules were seen, these were not diagnosed clinically. Even the smaller retinal vessels showed dilatation, thickened and infiltrated walls and proliferation of the intima and adventitia.

In his previous clinical analysis, von Hippel leaned to the theory of the tuberculous origin of the retinal disease. The pathologic examination led him to the conclusion that tuberculosis and, similarly, arteriovenous aneurysm must be excluded. He stated that the red spots were angiomas without, and the nodules with yellowish hue were gliomas with, glial proliferation. Similarly, Czermak interpreted the changes as angiomatous with glial proliferation of varying degrees. The glial proliferation is probably not present in the early stages, and it is therefore unnecessary to assume that the development of vascular loops leads to atrophy and disappearance of glia. Clinically, anastomosis of arteries and veins could not be demonstrated, as it was in the case of Jacoby, but the anatomic findings showed that such a possibility exists, and this would explain the similarity in color of the feeding vessels. The lesion of the vessel walls may be coordinated with or caused by the angioma, which represents a circulatory disturbance. The white spots and glittering patches are possibly produced by foam cells.

The anatomic study revealing the angiomatous nature of the disease in the case of von Hippel took place sixteen years after the lesion became established, and consequently secondary and reactive changes obscured

the picture. In the study of the sequence of changes early anatomic examinations are obviously of importance.

Ginsberg and Spiro [49] stated that the tumor consisted of vascular loops and glia—a typical angioma, with proliferation of adventitial cells of the endothelial channels, but with the accompanying glial proliferation tumor-like. The glial proliferation was to be considered as reactive only. There was no sharp demarcation between the glial and the angiomatous structures; either they were mixed or the glial proliferation penetrated into the angiomatous areas, in contrast to reactive proliferation, in which the glial and the connective tissue elements are sharply isolated. On the other hand, the cystic gliosis around the tumor, which led to penetration of the retina and choroidal adhesion, was of reactive nature, and occurred often without tumor formation. Considering that the constituents of the tumor were vascular loops and glial elements, the authors classified the tumor in their case as angiogliomatosis of the retina and stated that the glial proliferation present in Czermak's and von Hippel's cases were, similarly, not reactive but tumor-like. These observations agreed with Meller's clinical deduction so far as the glial proliferation was tumor-like, but disagreed in respect that the vascular proliferation was not tumor-like and the findings contradict the concept of vascularized telangiectatic glioma.

The pathologic studies of the 2 eyes examined by Griffith and Ormond [50] antedated those of Ginsberg and Spiro. The secondary glaucoma in their cases was the sequel to the intraocular angioid growth; the extensive detachment of the retina was due to the exudation. The mass between the retina and the choroid represented organizing hemorrhage, which alone would hardly explain as a primary defect the exudation and secondary changes present; but the assumption of disease of the terminal branches of the retinal vessels would suffice to furnish the proper background.

The first pathologic examination of the Vienna school was given by Guzman [51] in a case accompanied with iridocyclitis and secondary glaucoma. There was thickening of the nasal portion of the retina due to glial proliferation, the tissue consisting of oval nuclei embedded in waxy fibers. The proliferation of the vessels was considered as unimportant; they were present only in the inner layers, and the walls in part

49. Ginsberg, S., and Spiro, G.: Ueber Angiogliomatosis retinae (sogenannten von Hippelschen Krankheit), Arch. f. Ophth. **88**:44, 1914.

50. Griffith, A. H., and Ormond, A. W.: A Case of Massive Exudation of Retina with Arteriovenous Communication, Tr. Ophth. Soc. U. Kingdom **29**:279, 1909.

51. Guzman, E.: Zwei Fälle einer sehr seltenen Netzhauterkrankung, Ztschr. f. Augenh. **17**:40, 1907; von Hippelsche Netzhauterkrankung, Klin. Monatsbl. f. Augenh. **53**:242, 1914.

consisted of single-layered endothelial channels, and in part showed thickening of the connective tissue layer, with hyaline degeneration in some. Vacuoles and cystic cavities were present within the retina. The lamina basalis (vitrea) showed multiple perforations; there were proliferation into the choroid and sprouting of capillaries into the vitreous cavity. The temporal part of the retina showed similar changes, but of lesser degree, with moderate thickening of the membrane. Guzman and Fuchs accepted the glial proliferation described by Meller as the underlying pathologic process, but Fuchs noted the absence of glial staining in the specimen, which could prove conclusively the glial origin.

Emanuel's [52] patient, a 2 year old child, exhibited at the margin of the ciliary body and the choroid an almost circular tumor consisting of small vessels, the walls of which were formed by a single layer of cells, with some of the blood-containing spaces showing polygonal elements. The retinal vessels were greatly dilated and filled with blood; numerous retinal hemorrhages were visible. At the posterior pole the vessels were dilated, but in the anterior part the dilatation was of enormous degree and capillary proliferation was present. The endothelial proliferation was directed toward the lumen and the periphery, leading to complete occlusion of the lumens; occasionally capillaries with round cell infiltration of the adjacent tissues were noted. The retina showed colloid degeneration, corresponding particularly to the parts with pathologic changes in the vessels in the outer layers of the anterior portion of the retina. The homogeneous material was associated with the presence of vacuolated cells and cystic changes due to exudation, and extended into the subretinal space. The primary change was stated as an angioma of the ciliary body, proliferating into the anterior parts of the retina, which physiologically is poor in vascularization; the proliferation of the capillaries and of the large vessels was present in two different parts of the eye, which, according to the concept of Emanuel, testifies that the lesion is primarily multiple, and not metastatic, similar to the multiplicity of the lesions in neurofibromatosis. The angiomas of the retina show wide variations: In von Hippel's case there was angioma of the choroid with angioma and telangiectasis of the retina, according to Czermak, circumscribed angiomatous nodules projected toward the vitreous, and in Collins' [3] cases there was capillary angioma of the retina with telangiectasis, in 1 of 3 of which the proliferation even approached the cornea. The occurrence of tumors composed of vascular proliferations in parts other than the retina indicates that the primary changes are vascular, thus contradicting Mueller's assumption (based on clinical findings only) that the vascular changes are secondary in

52. Emanuel, C.: Anatomischer Befund bei einem Falle von Angiomatosis der Retina (von Hippelsche Krankheit), Arch. f. Ophth. **90**:344, 1915.

nature; similarly, the concept of Ginsberg and Spiro, that both glial and vascular elements are primarily involved, is untenable.

Gamper described a case of detached retina with compact tumors of the retina, the round central part consisting of convolutions of numerous vessels, occasionally suggestive of telangiectasis, with dilatations of small caliber. The individual vessels were of capillary character, being often only endothelial channels with or without an adventitia of connective tissue, and with only a sparse tissue separating the vascular elements. The capillary vessels were newly formed and intermingled with larger vessels; their relation to arteries or veins could not be established; they had a glassy adventitial layer and were separated from each other by a rich interstitial substance, composed mainly of connective tissue with some proliferating glial elements. The enormously dilated vessels were related to the tumor, but their differentiation as arteries or veins, like that of the vessels of smaller caliber, was extremely difficult. The greatest glial proliferation was evident adjacent to the vessels, with formation of cystic cavities filled with fibrin. The primary and pathognomonic changes were represented in the tumorous characteristics of the vessels, with the formation of small glomeruli, which consisted of convolutions of newly formed, small capillaries, with only a small amount of interstitial substance; these capillaries were seemingly connected with the smaller preformed and greatly affected vessels. The changes in the vessels consisted in thickening of their walls, due to a homogeneous proliferation of the adventitia cells, and endothelial proliferations leading to thrombotic obliterations of the lumen. The glial proliferation was of slight degree, without the destruction seen in gliosarcomatous proliferations or that which is often encountered with detached retina of long standing. The primary vascular character of the new growth was supported by a pathologist of the rank of Aschoff, in whose opinion the slides were representative of telangiectasis of the retina, analogous to vascular nevi of the skin—congenital malformations not restricted exclusively to vascular components of the skin, but affecting all other preformed elements, such as collagenous and elastic fibers, muscle elements and the structures of sebaceous glands. This concept furnishes ample explanation of the observation that vascular new formations of the retina are accompanied with neuroglial proliferation; furthermore, the multiplicity and absence of a destructive malignant growth were analogous characteristics.

The case of Miyashita and Nisyake [53] was classified as one of angiofibromatosis of the retina followed by general degeneration and closely

53. Miyashita, S., and Nisyake, Y.: Pathological Anatomy of Retinal Degeneration with Multiple Aneurysms, Brit. J. Ophth. **5**:448, 1921.

related to angiomatosis of the retina, but it is questionable whether it belongs to the type under discussion. The changes were in the lower temporal part of the retina close to the ora serrata; the vascular walls were degenerated, with dilatation and convolution of the vessels. The vascular changes were followed by hyperplasia of connective tissue and hemorrhages in the inner and outer retinal layers, destroying the external limiting layer. The extravasated, and almost completely defibrinated, blood spread between the retina and the choroid. The subretinal exudate was considered inflammatory, possibly secondary, due to degeneration and thrombosis of the vessels, with production of circulatory disturbance and resulting hemorrhage, transudation and migration of granular fat cells. The inflammatory origin could not be excluded, but the possibility of a hereditary vascular weakness was considered. At a comparatively early age, degeneration of the smaller vessels would appear, resulting in newly formed and convoluted vessels of inferior type and structure.

Brandt [54] studied 2 cases histologically, the first case being that of the son of von Hippel's original patient. In this case ghost cells were present with pigment in several layers at the choroidal surface and occurred in masses on the retinal surface; they were numerous in the subretinal space, pressing on each other and producing a honeycombed appearance. Cholesterol crystals had dissolved; only the characteristic imprints were visible. The tumor itself consisted of numerous capillaries, separated by delicate connective tissue, which stained pink with Van Gieson's method. But few of the vessels had open lumens or were filled with blood; most were obstructed by proliferating endothelial cells. The capillaries appeared either in cross or in oblique sections, producing accordingly the picture of stripes or compact masses when no lumens existed. There were vacuoles, the nuclei being either round or oval with mitosis. Carmine stains demonstrated a rich glycogen content not only in the tumor, but even in the adjacent retina.

In his second case, Brandt described slight hyperemia only in the posterior part of the choroid with normal pigment epithelium; groups of swollen cells similar to foam cells, were noted. Fibrinous exudate and proliferation of glia occurred in the retina, but not within the tumor. The tumor itself was surrounded by a delicate capsule of connective tissue with adjacent cystic cavities. In parts of the tumor with well formed capillaries filled with blood, the network was so dense that the vascular loops touched each other. In other parts the vessels were isolated by connective tissue. There were portions of capillaries not containing blood, solid stripes without any lumen and compact channels.

54. Brandt, R.: Zur Frage des Angiomatosis retinae, Arch. f. Ophth. **106**: 127, 1921.

Fatty degeneration, glycogen deposits and absence of ganglion and glia cells were established by special staining methods.

At the time of Brandt's study, von Hippel's original patient died, seven years after von Hippel had described his observations as angiomatosis of the retina, and autopsy revealed the presence of multiple blastomatosis, the tumors of the brain and bone marrow giving the impression of metastases of hypernephroma. Similarly, tumors were noted in the cauda, kidneys, epididymis and spleen, without the identification of a primary tumor. Multiple cysts in the kidneys, pancreas, epididymis, spleen and bones, cystic pancreas and multiple papillomas of the bladder were observed. There were similarities to von Hippel's illustrations of the retinal tumor, but their identity without the original slides could not be established. The explanation of the autopsy findings as metastases of the original retinal tumor seemed improbable considering the time element, seven years after the enucleation of the eye. The cysts of the kidney, the cystic pancreas and the papillomas of the bladder pointed, rather, to the possibility of primary multiple tumor formation, based on multiple anomalies and malformation of various tissues, a condition belonging to the group of dysontogenetic tumors, which are based on developmental disturbances.

In the analysis of the retinal changes, Brandt stated the belief that the vascular loops were the earliest manifestations and that the secondary gliosis prevailed only at the later stage. Meller mentioned vascular proliferations in glioma, but such an explanation is unacceptable for angiomatosis of the retina, because in gliosis of the retina the proliferation of vessels never reaches that in angiomatosis. Furthermore, primary gliosis of the retina or of the brain is not known to occur in young persons, and the secondary gliosis of the brain is always associated either with slow-growing tumors, as a result of vascular changes or of loss of nerve substance. Brandt emphasized that the retinal tumors have in common with angiomas of other parts of the body the vascular growth, but that a difference exists in that the angioma is congenital or the growth appears shortly in the period after birth and is progressive; furthermore, it is almost never symmetric, as is often the case in von Hippel's disease. Angiomas in other parts of the body are known to remain unchanged after the growth in the first year; the retinal variety is progressive. The angioma does not lead to irritation of the adjacent tissues; on the other hand, von Hippel's disease is characterized by an exudative tendency, even in the parts of the retina remote from the tumor. Angioma is not a destructive lesion. The destructiveness in von Hippel's disease, the exudative or degenerative changes in the retina, together with the late development, speak against its angiomatous nature. Brandt expressed his belief that the condition is an endothelioma. Endotheliomas and peritheliomas have a predilection for the brain and

meninges; they are familial and are primarily multiple, without metastatic tendency. Schieck [55] had published previously a case of perithelioma, which according to Ginsberg belongs to the group of retinal hemangioblastoma. Brandt called attention to the case of Sidler and Huguenin, that of an endothelioma, in which there was remarkable similarity to his description—numerous vessels and capillaries, mostly empty, and endothelial proliferation, leading to cellular membranes and a reticular arrangement of the tumor. On the other hand, Knodel [56] expressed doubt as to the endothelial nature of Brandt's tumors and stated that Brandt's description and illustrations did not warrant any conclusion other than hemangioma.

Heine [57] described the findings in both eyes in a case in which Berblinger independently reported the autopsy observations; strangely, their conclusions concerning the underlying pathologic process differed widely. In the left, the better eye, there was choked disk with cyst formation in the adjacent parts of the retina. The proliferating nuclei were said to be of glial and endothelial origin, and the proliferation was present not only in the retina but also in the optic nerve and its sheaths. Heine emphasized that the proliferation was not angiomatosis, or even angiosis, but, rather, was characteristic of gliosis. In the other, the poorer, eye, detachment of the retina, followed by glaucoma, was based on cyst formation within the retina. The retinal changes included the formation of small nodules, consisting of giant capillaries and small vessels with hyalinized walls and nodules, with surrounding proliferation of glial cells. Proliferation of the pigment epithelium and slight lymphocytic infiltration of the choroid were also noted. The process in this eye was also explained as gliosis, rather than as angiomatosis. In view of the relation of the gliosis to the vessels of the retina, the process was designated as angiogliosis, the two eyes representing different stages of the same lesion. The changes in the eyes and those of the spinal cord were not identical. The changes in the spinal cord represented angiomatous formations with glial reaction; the changes in the eyes were classified as nontumorous glial proliferation with slight vascular reaction. Accordingly, the changes in the spinal cord represented mesodermal and the ocular changes ectodermal, pathologic features. The ocular changes constituted an inflammatory pseudotumor with retinal cysts, the latter

55. Schieck, F.: Das Peritheliom der Netzhautgefässe, ein bislang unbekanntes Krankheitsbild, Arch. f. Ophth. **81**:328, 1912.

56. Knodel, G.: Zur Kenntniss der von Hippelschen Erkrankung (Angiomatosis retinae), Virchows Arch. f. path. Anat. **281**:886, 1931.

57. Heine, L.: Ueber Angiogliosis retinae mit Hirntumor (Capilläres Hämangiom), Ztschr. f. Augenh. **51**:1, 1923.

possibly to be explained as a defect in the germplasm, in view of the hemangioma of the brain.

Autopsy findings in the same case were reported by Berblinger,[58] who found the lower part of the medulla oblongata greatly thickened, and the tumor, visible grossly, reaching dorsalward to the tela choroidea of the fourth ventricle. In the surrounding parts four pinhead-sized cysts were noted. A cystic pancreas and cysts of the kidney were present. Berblinger's diagnosis was that of capillary hemangioma, in which the glial and ependymal proliferations were not of blastomatous nature; in view of the cystic changes in the pancreas and kidneys, the angiomatosis was thought to be of the nature of dysontogenetic blastomatosis. Berblinger mentioned the possibility of differentiating hemangioma and hemangioendothelioma. In both tumors the blastomatous tissue arises in the capillaries, but in the first the formation of new vessels and in the second the endothelial proliferation dominate the picture. In hemangioendothelioma the prolific and versatile endothelium gives rise to the rounded perivascular cells; in addition to their heaping up within the lumens they may invade the walls and proliferate outside. In cases of hypertrophic hemangiomas it may be difficult to demonstrate the lumens of the proliferating capillaries, but in hemangioendothelioma the intravascular and perivascular proliferation of the endothelial cells is associated either with new formation of capillaries or with ectatic varieties of the preexisting ones. The hemangioendothelioma is less differentiated and therefore possesses a malignant tendency. Berblinger did not accept the neoplastic character of the glial proliferation in his case; rather, he regarded the process as that of reparative gliosis. Even assuming the possibility of glial tumor, the capillary angioma and the glioneuroepithelioma would be independent of each other. According to Berblinger, the changes in the eye belonged to the group of angiomatosis of the retina; anatomically, the changes did not represent glioma telangiectodes. He considered the early stages of glial proliferation of von Hippel disease as angiomatosis, with the possibility of blastomatous glial proliferation in the late stages; this late stage may represent an angiogliomatosis but does not comform with Heine's designation of angiogliosis, for the latter term fails to take account of the tumorous character.

The clinical and pathologic evaluation in the early period seemed to be hopelessly confused, since at the time all vascular growths of the central nervous system were designated as angiomas in spite of their grossly dissimilar characteristics. Cushing and Bailey were the first to clarify the confused issues, dividing the vascular growths into two

58. Berblinger: Zur Auffassung von der sogennanten von Hippelschen Krankheit der Netzhaut, Arch. f. Ophth. **110**:395, 1922.

groups, angiomatous malformations and hemangioblastomas, or genuine neoplasms of the blood vessel elements, and composed solely of mesodermal tissues. The true character of the latter is revealed by invariable presence of traces of compressed nerve tissue between the vascular loops of the lesion. This differentiation into two groups was a great advance, as they differ distinctly as to site, symptoms and anatomic structure, and only rarely were objections raised; Junius, however, expressed the belief that the two groups represent only developmental varieties of congenital vascular anomalies and that the division depends on what one understands by the concept of blastomatosis.

According to the classification of Cushing, the angiomatous malformations are capillary (telangiectatic), venous (angioma venosum) and arteriovenous. The neoplastic vascular growths, called hemangioblastomas by Cushing and Bailey,[59] are identical with the angioreticulomas of Roussy and Oberling, and Lindau designated them as angioblastic tumors. The designation of Lindau bears the important implication that they are not angiomatous malformations, but primary vascular new growths. Lindau broadened the concept of purely local vascular disease into the syndrome of angiomatous cystic growths in various parts of the body. Later studies revealed the hereditary nature of the disease, with variations of expression, the full syndrome alternating with less pronounced clinical manifestations and absence of some of the components within the same family tree. This wide variation in the syndrome is due to the association of an autonomously growing angioma of the retina or central nervous system with dysontogenetic changes in the abdominal organs on a hereditary basis. The phenotypical manifestations in the organs of the various members of the family show a notable divergence. In the individual member the single symptom may be suppressed or accentuated.

Lindau was first to recognize the composite syndrome, the concomitant occurrence of angiomas of the retina and central nervous system with vascular cysts of various viscera, cystadenoma of the pancreas and carcinoma (hypernephroma) of the kidney. Furthermore, Lindau called attention to the fact that the lesions are frequently multiple, give symptoms only in adult life and occur with predilection in the hindbrain. The favorite site was given as the cerebellum, the medulla oblongata or the cord being sometimes involved. Later observations proved that the cerebrum is rarely affected, and only as an exception (Rochat, Keller).

59. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Haemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

The congenital theory of the origin of hemangioblastoma seems to be favored by most investigators. Karlefors [60] showed that in the third month of fetal life a vascular mesenchyme is present on the posterior medullary velum. The cerebellar hemispheres also begin to develop at this time, and, according to Lindau, part of the original vascular mesenchyme lying on the posterior medullary velum may be drawn into the cerebellar hemispheres. The midline position of the tumors is explained by the original position of the primary vascular plate. From the vascular mesodermal roof plate, the anlage of the local meninges and the vascular plexus of the fourth ventricle develops. The presence of extracerebral neoplasms is similarly based on congenital rests or malformations of the embryonic mesenchyme, as the vascularization of the retina and the ingrowth of mesodermal elements into the pancreas occur similarly in the third month of the fetal life. The embryonal retina, arising from the central nervous system, is covered with mesenchyme. With the invagination of the optic cup this mesenchyme gives rise to vasoformative tissue, which, it is believed, eventually degenerates. The absence of pia-arachnoid membrane covering the retina would indicate that the hemangioblastoma arises from the vasoformative elements within the primitive mesenchyme. Whether membrane-formative elements (giving rise to covering membranes of the retina) or vasoformative elements (giving rise to blood vessels) are implicated cannot be decided, but the formative tissues develop originally from the endothelial primordium within the mesodermal layer. Likewise, the cysts of the kidney may be explained on the basis of contemporary maldevelopment. Grinker's opinion concurs with Lindau's, namely, that the hemangioblastoma with secondary slight reactive glial proliferation arises from the rest of the primordial angioblastic mesoderm and may form undifferentiated hemangioendothelioma or more complicated capillary or cavernous hemangioblastoma.

Lindau gave the favorite site of occurrence of tumors as the cerebellum, rarely the medulla or the spinal cord. In the cerebellum a large cyst is often formed, and only careful study will detect a small mural nodule, the hemangioblastoma. Microscopically, it may appear vascular or avascular, and is often yellowish, due to its lipid contents. The lesion may be compact and encapsulated, and frequently more or less cystic. The cyst may be situated in the tumor or in the adjacent tissues and is most commonly a single large cyst with a mural nodule. Microscopically there is a sharp demarcation between the tumor and the nerve tissue. The tumor is composed of blood vessel elements, forming

60. Karlefors, J.: Die Hirnhaute des Kleinhirns, Stockholm, P. E. Norstedt & Soener, 1924.

vascular spaces and channels with abundant intercapillary tissue and swollen, fat-laden endothelial cells. In the case of a highly cellular tumor and indistinct capillary spaces the proper recognition may be extremely difficult. Cushing and Bailey [61] pointed out that silver staining methods (Perdrau) demonstrate a rich network, which is peculiar to these tumors and points to their mesodermal origin. The fat-laden xanthomatous cells are not degenerative, but their appearance is due to circulatory disturbance accompanied with stagnation of lymph rich in lipids; the phagocytic activity of the endothelial tumor cells transforms them into foam cells.

A striking feature of the tumors is the tendency to cyst formation; there is a marked exudative property, producing a plasma transudate. The cyst may be within the tumor, but more frequently without, in the adjacent nerve tissues. The explanation is probably that the nerve tissue, owing to the lack of lymphatic channels, cannot dispose of the fluid produced by the angioma and reacts therefore with cyst formation.

Lindau noted that hemangioblastoma bears resemblance to other heredodegenerative diseases associated with tumor formation and developmental anomalies of the central nervous system, such as tuberous sclerosis (Bourneville) and neurofibromatosis (von Recklinghausen). In the first condition (Lindau) the disturbance is in the mesodermal development; in the last two, in the ectodermal development.

The correlation of tumors of the central nervous system and those of the retina due to an underlying early maldevelopment, and their coordination with malformation or tumors of the somatic organs, is a feat credited to the insight of Lindau. It is only regrettable that some of the observers proposed to call the retinal angiomatosis von Hippel's disease, and the involvement of the central nervous system (with hereditary connections in the first group) Lindau's disease. This division into two groups not only minifies the credit due Lindau, but is misleading, as there are cases in which only autopsy demonstrated the presence of a typical cerebellar lesion and the subsequent examination of the retina revealed an identical pathologic process in the formerly unsuspected retina. For instance, Cushing and Bailey [61] reported 11 cases of cerebellar hemangioma, and reexamination in 1 of the cases revealed a typical angioma with advanced exudative patches in the deep layers of the retina.

After Lindau's observation, Wohlwill,[62] on the basis of 16 of his own cases and of 24 cases collected from the literature, reported a

61. Cushing, H., and Bailey, P.: Hemangiomas of Cerebellum and Retina (Lindausche Disease), Arch. Ophth. **57**:447, 1928.

62. Wohlwill, A.: Ein Fall von Angiomatosis des Zentralnervensystem (Lindausche Krankheit), Zentralbl. f. d. ges. Neurol. u. Psychiat. **46**:456, 1927.

tumor in the roof of the fourth ventricle and the spinal cord with cystic cavities, tumor of the retina, cystic pancreas, hypernephromas and cyst of the kidneys and called attention to the association of capillary angiomas of the spinal cord with syringomyelia. Schley [63] reported 2 cases at about the same time. Schuback's observation has added interest because the retinal tumor was discovered only at autopsy, which also disclosed the presence of capillary angiomas in the fourth ventricle and the spinal cord. All the tumors were of similar structure. The main constituents of the tumors were delicate capillaries, consisting mostly of single layers of endothelial cells, sometimes with slight connective tissue. Vascular sprouting was frequent, the lumens either being collapsed or filled to capacity with blood. The tissue between the loops showed an extremely rich content of small cells with round or oval nuclei, occasionally so numerous and uniform in appearance as to suggest sarcoma, but the sharp outlines of the tumors testified against the latter possibility. The low degree of differentiation was conspicuous in the projections of the tumor of the ventricle, where the endothelial cells were hardly discernible; the spindle-shaped cells recalled only faintly the endothelial type. Cells saturated with fat droplets, pseudoxanthoma cells, showed double-refracting substances with polarization apparatus. Syringomyelia was present, and Schley called attention to the fact that in 4 of 15 cases of capillary angioma tumor formation was associated with this condition, and that this relatively frequent association, in view of its rare occurrence in the cavernous type, suggests the possibility of a relation to the dysraphic group.

The keen observation of Lindau proved that isolated retinal lesions are not chance occurrences but constitute a disorder *sui generis* with hereditary tendencies; in 1 of his cases an angioma of the peripheral retina was revealed only on histologic examination, after autopsy had disclosed the typical systemic disease. Cushing and Bailey accepted Lindau's explanation, but Meller and Marburg came to a widely different conclusion.

Meller and Marburg's [64] patient, a man aged 23, whose father died of cerebellar tumor and who was under observation for a similar condition, had had poor vision in his left eye for three years. The disk was red; the upper temporal pair of vessels was enormously dilated; the artery was beaded and aneurysmal. Above the disk small white patches were visible; above the macula the patches were circularly arranged, with a few dots extending downward from the macula. The tortuosity of the vessels increased toward the periphery and led to a

63. Schley, W.: Ueber das Zustandekommen von Gehirncysten mit gleichzeitiger Geschwulstbildung, Virchows Arch. f. path. Anat. **265**:665, 1927.

64. Meller, J., and Marburg, O.: Zur Kenntnis des Wesens der sogenannten Czermak-von Hippelschen Netzhauterkrankung, Ztschr. f. Augenh. **66**:1, 1928.

large, red, sharply outlined, bulging spot, with the vessels disappearing within the spot. In the adjacent part of the retina small red patches were noted. Autopsy revealed the typical cyst of the cerebellar hemisphere with mural nodule, which was grossly diagnosed as cystic glioma, the exact nature being undetermined because the specimen was lost.

The cyst formation within the retina spared the inner plexiform, ganglion and nerve fiber layers; the content of the cyst was pink, but with staining for glial tissue a fibrinous network was disclosed. The cyst therefore differed from cysts described by Blessig, which are located at the ora serrata and are always empty.

According to Meller and Marburg, the cells in the multiple tumors were not endothelial, but were derivatives of Müller fibers, both bipolar and polygonal. The nuclei were identical with those of Müller's fibers. The origin of the cells in the inner granular layer was the Müller fibers; in the fiber layers there was blastomatous proliferation of the glia cells. Many of the nodules exhibited poor vascularization, and one of them was avascular, evidence against the possibility of angioma. Pathognomonic of the disease is the benign proliferation of the glia, a gliosis, in contradistinction to glioma. The diffuse glial proliferation is predominant; angiomatous nodules are few. In the dense nodules the glial proliferation is lacking; between the loose nodules it is rich. The vascular overgrowth is not a primary, but a secondary phenomenon.

There is a wide discrepancy between Lindau's description of the early stages and their consequent interpretation and that of Meller and Marburg. Lindau described the early stages of the nodule as follows:

> The tumor was nearly twice as large as a glomerulus and strikingly resembled one in appearance. It was made up of large endothelial cells, forming wide capillaries, richly filled with blood. There was no evidence of circulatory disturbance, small giant cells or pseudoxanthoma cells, so far as one could tell without special staining for fat. The tumor was sharply limited from the surrounding retinal tissue, which was somewhat vacuolated. The growth had obviously begun in the inner layers of the retina and had compressed both nuclear layers into one. The tumor where it was the largest included the entire width of the retina and caused the internal limiting membrane to bulge into the vitreous. Glial staining revealed no element of gliosis in the tumor. The growth was purely mesodermal, and even in the neighborhood of the tumor there were no signs of a gliosis reaction.

Meller and Marburg described a nodule of almost exactly similar size and position as follows:

> A third, very small nodule, lying in the nerve fiber layer, was approximately 0.25 mm. thick, produced bulging of the ganglion cell layer and rose a little above the general retinal level. This nodule was very rich in cells; it contained no vessels, and even in its neighborhood no vessels were to be found. The cell nuclei showed only pale staining; they were sometimes round, sometimes long and of variable size. Some nuclei showed a bipolar cytoplasm. The nodule, owing to its richness in

cells, was sharply differentiated from its surroundings. Normally, only a few nuclei belonging to neuroglial cells are found in the nerve fiber layer. It was through an overgrowth of these cells that this nodule was formed.[64]

The almost identical early stages of the nodule have been variously characterized. Von Hippel had already observed that connective tissue formation between the vascular loops is more frequent than glial proliferation and called attention to the difficulty in differentiation of glial hyperplasia and gliosis. Brandt failed to note glial proliferation, and Gamper saw proliferation of fibrillar glia only around the large vessels. Ginsberg and Spiro and Bergmeister occupied an intermediate position in accepting the concept of the new formation of the glia. Next to endothelial channels with proliferating endothelium, they observed xanthoma cells and cells appearing as glia. Ginsberg and Spiro did not deny the angiomatous nature but assumed the association of glial and endothelial proliferation. Angiogliomatosis should represent a transition between the purely glial and the almost purely capillary proliferation. The majority of authors following Lindau did not give much credence to the theory of glial explanation; most of the observers agreed that the glia does not actively participate in the tumor formation, and occurs only as a reactive gliosis in the surrounding parts and in the formation of mural angiomatous cysts. Meller and Marburg's interpretation of angiogliomatosis, according to Lindau, was incorrect, as Bailey's reinvestigation of their slides did not confirm their opinion. Similarly Cushing and Bailey did not accept Roussy and Oberling's [65] interpretation of their observations as angiogliomatosis, a mixed tumor consisting of capillary angioma and glioma. Jess's [66] opinion of angiogliomatosis could not be verified by Lindau, who, after studying the aforementioned slides, declared that the findings were typical of angiomatosis.

In Sargent and Greenfield's [67] 7 cases of cerebellar cyst retinal angiomatosis was not a complication. The close relation of cerebellar cyst to trauma of the head was established clinically in some cases, but it is probable that the trauma may initiate the cyst formation where an angioma of the cerebellum was preexistent. The existence of a simple developmental cerebellar cyst is doubtful. In 1 of their cases such an angioma was at first overlooked, owing to the minute size of the lesion in a dimple of the wall of the rather large cyst.

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65. Roussy, G., and Oberling, C.: Les tumeurs angiomateuses des centres nerveux, Presse méd. **11**:179, 1930; J. Nerv. & Ment. Dis. **77**:457, 1933.

66. Jess, A.: Angiogliomatose der Netzhaut und Gliom der Rückenmarkes, Concilia ophthalmologica, Tr. Internat. Cong. Ophth. **2**:615, 1938.

67. Sargent, P., and Greenfield, J. G.: Haemangiomatous Cyst of Cerebellum, Brit. J. Surg. **17**:84, 1929.

Lindau's clarification of the pathology of tumors of the retina and central nervous system made a deep and lasting impression, as the literature of the ensuing years testifies. Paton, Williamson-Noble and Greenfield [68] studied one eye of a patient in which unorganized serous effusion raised the retina; the tumor was attached to the choroid and penetrated through the retina into the vitreous. The tumor represented a rounded mass of angiomatous tissue surrounded by a zone of neuroglial overgrowth, almost gliomatous in appearance. The neuroglial component almost equaled the tumor in width and surrounded it on the inner surface of the choroid, extending inward to the outer surface of the retina, which was displaced inward by the growth. The tumor measured 3 mm., was located in the posterior part of the globe and consisted of a plexus of delicate capillary vessels with fine connective tissue walls and large, oval endothelial cells; the vessels were mostly empty or occasionally contained a few red blood corpuscles. Staining for glia proved the absence of neuroglial fibers or recognizable nerve elements within the angioma. In striking comparison to the tumor, the circle of neuroglial overgrowth consisted of neuroglial fibers arranged in bundles and whorls. Foam cells or phagocytic elements were not observed around the tumor, but several of the large veins were surrounded by cuffs of lymphocytes many cells in thickness. From a study of the slides, it was difficult to decide whether the tumor was essentially neuroglial or angiomatous, and, furthermore, whether the neuroglial ring should be regarded as tumor or as reactive tissue. Since cerebellar tumors do occur with neuroglial tissue within the angioma, the authors assumed that the tumor was a true capillary or plexiform angioma, just as in congenital conditions the neuroglial overgrowth may be neoplastic or reactive, without any essential distinction between the two forms.

The difficulties of the histologic diagnosis and interpretation were vividly demonstrated by Sladden.[69] The case had been described about twenty years previously by Thomas and Coats [70] as one of a "peculiar granuloma of the retina," without definite classification. Autopsy revealed two soft tumors—one pedunculated, external to the left cerebellar lobe, subdural and pressing into the lobe, and the other, smaller, in the posterior part of the right cerebellar lobe. The left kidney revealed the presence of two small black tumors. The autopsy observation warranted renewed study of the eye, which led to the classification of angioma, with an unusually high proportion of endothelial cells and

68. Paton, L.; Williamson-Noble, F. A., and Greenfield, J. G.: Capillary Angiomatosis (Lindau), Tr. Internat. Cong. Ophth. **2**:624, 1929.

69. Sladden, A. F.: A Case of Lindau's Disease (Capillary Angiomatosis), Brit. J. Ophth. **14**:224, 1930.

70. Thomas, F. G., and Coats, G.: A Peculiar Granuloma of the Retina, Tr. Ophth. Soc. U. Kingdom **31**:149, 1911.

relatively slight formation of blood spaces. The retinal growth was not encapsulated but was sharply defined and situated just to the side of the disk. It was highly cellular; in a few places it was composed only of endothelial channels, and in others it was highly vascular with well formed vessels. The tumor cells were mostly elongated, with oval or sickle-shaped nuclei, which were closely packed and obscured the supporting stroma. The constituent cells were devoid of mitotic figures, characteristic of sarcomas. The cerebellar and renal tumors were less densely cellular; the cells were more pleomorphic than those of the retina. The most concentrated areas showed nuclei similar to those of the retinal tumor and absence of mitotic figures. Fibroblastic cells contributed to the structure of the walls and blood spaces. The hemangiomatous nature of the tumors was more evident in the cerebellar growth. Greenfield [71] accepted the current opinion that the hemangioma is a tumor or malformation of congenital origin, that its growth during life is limited and that occasionally it may show progressive growth and become sarcomatous, being mesoblastic in origin. The possibility of sarcoma was suggested by the case of Sladden; however, according to Greenfield, the absence of mitotic figures, excluded this possibility.

Rochat's [72] study not only shed light on the hereditary tendency of the disease, but demonstrated the histologic structure of the retinal tumors in two members in two successive generations of the same family; furthermore, it provided evidence that such tumors of the brain are not necessarily confined to the cerebellum, but may occur in the cerebrum as well. In the first eye he observed (that of the third brother of the second generation, the second member with angiomatosis of the retina) the entire retina was thickened, one enormous nodule reaching from the ora serrata to the disk, with a large cyst behind the equator. There were numerous smaller nodules, the largest being in close proximity to the lens. The structure was more evident in the smaller nodules—capillaries with walls of a single layer of endothelium, the endothelial cells being enlarged and the lumens containing blood. Between the capillaries delicate connective tissue was visible. In some places the capillary structure was clearly discernible, with larger interspaces and collar-like hyaline connective tissue around the vessels. In the larger nodules the masses were more compact; the constituents, the smaller vessels, were not easily visible. Nevertheless, numerous lumens with blood corpuscles were discernible, but the endothelial proliferation led to the constriction of the lumen; the proliferating capil-

71. Greenfield, J.: Discussion, Tr. Roy. Soc. Med. **24**:383, 1930.

72. Rochat, G. F.: Familiäre Angiomatosis retinae und Kleinhirnangiom, Klin. Monatsbl. f. Augenh. **78**:601, 1927; Grosshirnangiom bei der Lindauschen (von Hippelschen) Erkrankung, ibid. **86**:23, 1931.

laries were in close contact, veiling the original capillary structure. Occasional large lumens, much larger than are ever seen in the normal retina, corresponded to the ophthalmoscopic picture. The second eye (that of a member in the third generation, the oldest son of a normal sister) revealed a similar retinal tumor formed of a dense mass of hypertrophic capillaries with remnants of degenerated retina in the glial tissue.

In the third eye (that of the third brother of the second generation, who had choked disk and had previously undergone trephination of the skull for relief of cerebral symptoms), microscopic examination of the retinas did not disclose the presence of angioma. Autopsy revealed tumors of identical and typical structure in the cerebellum and in the cerebrum.

Angioblastic tumors are usually not encountered in the brain but are found only in the cerebellum, spinal cord and brain stem. Lindau expressed doubt whether true hemangioblastomas ever occur in the cerebral hemispheres, and Cushing and Bailey did not encounter any in their extensive material and were reluctant to accept cases described in the literature under various designations as true instances of this type of neoplasm in the cerebrum. They described cases of supratentorial angioblastic tumors which they considered as arising in the meninges, and they designated these growths as angioblastic meningiomas. Rochat's case, therefore, is of the utmost importance. It occurred in the third generation of a family with numerous cases of hemangiomatosis of the retina and central nervous system; furthermore, the cerebral angioblastic tumor was associated with three intracerebellar hemangioblastomas of identical structure. It occupied the basal half of the temporal and occipital lobes; it was cystic, intracerebral and well demarcated, contained pseudoxanthoma cells and therefore must be considered a verified hemangioblastoma of the cerebrum. It is not clear from the description whether the tumor reached the surface, and it may possibly have had a dural attachment.

In Keller's [73] case the tumor was a large cystic lesion; the author emphasized the absence of a dural attachment; however, the tumor was intimately related to the pia of the sylvian fissure. Histologically, the tumor was rather characteristically a capillary hemangioblastoma, like Rochat's, and therefore both cases must be accepted as rare manifestations of supratentorial hemangioblastoma. In Keller's case the capillary angiomas were multiple in the left temporal lobe. Whereas in Rochat's case only cystic cavities were present, in Keller's case a large cyst was found. Keller noted that the cells described by Lindau were

73. Keller, H.: Sogennante "hyperplastische Kapillarangiome" (Lindau) und Grosshirncyste, zugleich ein Beitrag zur Tumorcystenfrage, Virchows Arch. f. path. Anat. **289**:151, 1933.

light, large and poor in chromatin; in his case, next in frequency to this type was a round or oval cell, rich in chromatin, and apparently with shrunken nuclei. The cells of the first type were young connective tissue cells, the perithelioma-like structure around the larger capillaries and the cavities denoting their origin from the connective tissue of the adventitia. The cases of Rochat and Keller prove that supratentorial tumors occur in the form of cerebral hemangioblastomas, similar in origin to cerebellar hemangiomas.

Seidel [74] studied the eye of a patient who was the daughter of the original patient of von Hippel (included in the article of Brandt) and whose brother was similarly affected. The patient's left eye presented the typical changes of angiomatosis retinae. Clinical inspection showed choked disk in both eyes without tumor formation, but microscopic examination disclosed two small tumors lying in the nasal periphery of the retina, without lifting the retinal level, and situated in the nerve fiber layer with slight dislocation of the inner granular layer. The tumors consisted of convolutions of numerous capillaries, part of which were empty and part were filled with blood. Between the loops hyalinized connective tissue, with endothelial-like cells with oval nuclei, was visible. Otherwise the retina was normal, without any inflammatory signs; cystic degeneration of the retina occurred only in the nasal, and not in the temporal, part. Vessels were extremely dilated, resulting in bulging of the internal granular layer with glial proliferation, and cross section showed occasional slight inflammation with perivascular accumulation of lymphocytes. The left eye presented two small tumors in the temporal part close to the ora serrata, with cystic degeneration of the retina. The tumors were more prominent than in the right eye, were similarly situated in the nerve fiber layer but extended into all layers, reaching the external granular layer. The congenital anomaly at the disk, observed ophthalmoscopically, consisted of a capillary net. In both eyes the lesion was doubtless a primary angioma with reactive glial proliferation. The autopsy observations form the substance of Knodel's report: cystic tumor of the pons and medulla oblongata, cyst with mural angioma, cystic cavities with syringomyelia, angioma of the left adrenal gland and cystadenoma of the right kidney with pearly cyst degeneration. Knodel stated that the glial proliferation was reactive, and that the tumor formation was angiomatous without glial proliferation of neoplastic nature. The tumor in the medulla oblongata represented angioma with fibrillary glioma and cystic cavities, a purely mesenchymal tumor with participation of ectodermal elements, but not a mixed tumor, for the two cell constituents were not represented in all

74. Seidel, E.: Anatomische Frühstadien der Angiomatosis retinae (von Hippelsche Krankheit), Verhandl. d. deutsch. ophth. Gesellsch. **49**:535, 1932.

parts of the tumor. The formation of the tumor was that of a "collision tumor" (R. Meyer); with intermingling proliferations at the point of the juncture of the two histogenetically different elements, but only at the points mentioned. Otherwise, the angiomatous nature of the tumors was the typical one.

Analogies of retinal hemangioblastoma to tuberous sclerosis and neurofibromatosis, as mentioned before, did not escape the attention of Lindau. Van der Hoeve [75] proposed the designation of phakomatosis (1932) for the three aforementioned diseases, to which years later the Sturge-Weber disease was added. The four constituents of the group are separate entities with sufficiently numerous differences, yet possess so many points of resemblance as to suggest that all belong to the same group of anomalies. The common denominators are the hereditary character and the fact that the various anomalies are not restricted to one germinal layer exclusively, though each shows predilection for one germinal layer and attacks this layer chiefly (angiomatosis, mesodermal; tuberous sclerosis, ectodermal). The birthmark, phakoma, may be present at birth or develop later in life, it may be small or large. The designation "phakoma" was selected to differentiate it from nevi of the skin or pigmented moles of the iris and retina, which contain nevus cells. The phakoma may proliferate into tumors containing glial derivatives of primary or secondary (reactive) nature. These phakomas are malformations resembling blastoma, and phakoblastoma is a genuine new growth with malignant possibilities. Van der Hoeve refused to consider the proposition of Putchar,[76] who suggested Albrecht's designation of hamartoma, as hamartoma and christoma are only subdivisions of phakomatosis. Loewenstein and Steel,[77] in agreement, considered tuberous sclerosis as a primary ectodermal malformation, the disturbance of balance of ectoderm and mesoderm leading secondarily to a mesodermal tumor. The reverse sequence is at work in angiomatosis, in which the primary growth is mesodermal and the secondary growth ectodermal. The phakomatoses are based on the proliferation of undifferentiated cells in one germinal layer, with disturbance of the mutual pressure of tissues needed for normal development. The same mechanism

75. van der Hoeve, J.: Eye Symptoms in Phacomatoses, Tr. Ophth. Soc. U. Kingdom **52**:380, 1932; Eine vierte Phacomatose, Verhandl. d. deutsch. ophth. Gesellsch. **57**:136, 1936. Brouwer, B.; van der Hoeve, J., and Mahoney, W.: A Fourth Type of Phakomatosis (Sturge-Weber Syndrome), Nederl. Acad. Wetens. **38**:33, 1937. van der Hoeve, J.: Phakomatoses, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, p. 124.

76. Putchar, W.: Ueber Angiomatosis des Centralnervensystem und der Netzhaut, München. med. Wchnschr. **82**:1384, 1935.

77. Loewenstein, A., and Steel, J.: Retinal Tuberous Sclerosis (Bourneville's Disease) Am. J. Ophth. **24**:731, 1941.

is responsible in the four clinically very different-appearing diseases. One of the differences lies in the fact that tuberous sclerosis and hemangiomatosis are not known to cause hydrophthalmos.

Carr and Stallard [78] described a poorly vascularized mass arising in the retina, consisting of endothelial and glial elements, with cystic spaces filled with fibrin, lymphocytes, leukocytes and detritus at the surface of the tumor, and diagnosed the changes as angiomatosis. Junius [79] refused to accept the concept of hemangioblastoma proposed by Cushing and Bailey; namely, that the angioma is a hyperplastic process, the result of angiomatous malformation, in which the lack of development of the capillaries leads to compensatory dilatation of the vessels with aneurysms to regulate the circulation, an opinion accepted only by Smelanski. Junius cited Borst, in whose opinion angiomatosis of the retina is telangiectasis (hamartoma) occasionally associated with glial proliferation (angiogliomatosis), but he added that, according to B. Fischer, the angiogliosis of the retina is neuroblastomatous. Fischer pointed out the differences between cerebral and retinal gliomas: The first is relatively benign, arising in later life and not metastasizing; the second malignant, arising at an early period and giving rise to metastases. The glioma of the retina derives from primitive neuroblast, similarly to the neuroblastomas of the sympathetic nervous system. The same relation which characterizes the gliomas of the two organs should, according to Fischer, exist in the von Hippel–Lindau disease.

The difficulty in making the histologic diagnosis is further demonstrated by the case originally published by Schieck as an instance of perithelioma. The tumor was at the disk, and was sharply outlined, the retinal vessels appearing at the margin of the tumor. The low power lens revealed an intimate relation to the central vessels but sharp isolation from the nerve tissues. Higher magnification showed that the tumor was not a solid mass, but contained numerous delicate blood-containing spaces in the form of slits, forming a system of channels of very small caliber, surrounded by the tumor. The channels had an endothelial lining. Spindle-shaped cells with slender nuclei occurred in parts where the cells were closely packed; in other parts epithelial cells with good protoplasm formed a mosaic of polygonal cells, recalling the picture of a flat endothelial surface. The form of the cells suggested the proliferated elements of vascular walls, a resemblance which

78. Carr, T. A., and Stallard, B. H.: Angiogliomatosis of the Retina, Brit. J. Ophth. **17**:525, 1933.

79. Junius, P.: Bemerkungen zum Krankheitsbilde der "Retinitis" (Coats), der Netzhautdegeneration mit multiplen Aneurysmen (Leber) und der sogenannten "Angiomatosis retinae" (Czermak–von Hippel), Ztschr. f. Augenh. **68**:207, 1929; Venöse und arterio-venöse Angiome im Bereich des Gehirns: Ihre Beziehungen zum Sehorgan, Zentralbl. f. d. ges. Ophth. **29**:673, 1933.

became more evident in their relation to the central vessels. These vessels showed a normal intima but the adventitial cells were proliferated, with typical young tumor cells of embyronic type. The spindle cells disclosed forms transitional to polygonal cells, which were the constituents of the tumor with the endothelial appearance. No proliferation of glial or neural elements was noticeable. This perithelioma of Schieck was reexamined by Putchar and classified as hyperplastic capillary angioma of poor vascularization, probably with proliferation of cells in the neighborhood of the vessels. The atypical histologic appearance and the absence of foam cells with lipid deposits, in conjunction with the unusual location of the tumor, were responsible for the misinterpretation of the real nature of the tumor. Appelmans explained his case as one of primary angioma, but the difficulty of histologic classification similarly existed in his case, as it was not possible to demonstrate with certainty the angiomatous, the glial or the mixed origin of the tumor.

Jung [80] mentioned that cerebellar angioma is an extremely rare tumor, as only the cavernous type had been noted. In 1922 Lechner could collect only 3 cases from the literature; the number has risen to 80 since Lindau's work has become known. Of Jung's 7 cases, only 1 showed the combination with retinal tumor which was the subject of Lotman's study. In all but 1 of Jung's cases cerebellar cyst was present with the tumor. The cysts were smooth walled and contained yellow fluid, which coagulated on fixation. The tumors were red, or yellow in case of fatty degeneration; they were punctated by smaller and larger holes, corresponding to the opening of the vessels, in a manner similar to that in the retina. The tumors were small, benign and of slow growth. The rapidity of appearance of clinical symptoms depends on the expansion of the cyst. The angiomatous nature is not easily visible in all cases; often, with the usual stains they simulate a richly vascularized glioma. The vascular origin is demonstrated by silver and gold impregnations (Perdrau, Achucarro, Ramón y Cajal); numerous vessels and capillaries and a dense network of reticular fibers surround the intermediate cells. The capillary structure is easily detected in the younger parts, i. e., at the periphery. The network is characteristic without being specific. Gliomas and gliosarcomas may show a similar arrangement of fibers, since mesodermal elements participate in the formation. Gliomas and the tumors of tuberous sclerosis are known to have angiomatous portions. The question is complex, suggesting a common growth of glial and mesodermal elements; glial and connective tissues are genetically distinct, but functionally closely

80. Jung: Ueber die Angiome Lindaus als eine charakteristische Gruppe unter den Kleinhirntumoren, Arch. f. Neurol. u. Psychiat. **103**:581, 1935.

related. The role of connective tissue in gliomas is not clear; but immature gliomas and ependymomas contain delicate argyrophilic nets (Schaltenbrand and Bailey); and, according to Hortega, in heteromorphous gliomas the hyperplastic connective tissue not only surrounds the vessels but forms large nets. In retinal angiomatosis strong participation of the glia was observed; it was considered important by only a few observers, and as secondary by the majority. In 1 of Jung's cases (similar to a case of Roussy and Oberling's) the glial proliferation was evident and could not be relegated to a secondary role. Nevertheless, the separation of angioglioma in this type is unwarranted. In 2 of his cases there was not only reactive proliferation, but simultaneous proliferation of both the vascular and the glial elements. Lotman,[81] describing the eye in a case of retinal angiomatosis of Jung's, mentioned the possibility of a type, associated with dysgenesis and blastomatosis of the central nervous system, in which capillary angiomatosis is associated with primary gliomatosis and secondary cystic formations (with no genetic relation to angiomatous formations) or syringomyelia, bringing in close connection the pathogenesis and status dysraphicus.

The true nature of angiomatosis of the retina, a mesodermal neoplasm arising primarily from the vascular elements, has become recognized with increasing frequency by the majority of observers. Collins,[82] in a later study, agreed with the belief expressed by Cushing and Bailey, namely, that these lesions, composed of fully formed vessels, scarcely deserve to be regarded as tumors; the angiomatous malformations and those composed of cellular elements of the blood vessels represent neoplasms, the angioblastomas. Collins made a similar division of the vascular lesions of the retina: Group 1: retinal angiomas, consisting of fully formed retinal vessels with or without association of hemangiomatous involvement of the skin or mucous membranes. Group 2: an immensely enlarged pair of vessels (artery and vein) leading to a mass, usually in the periphery of the retina, composed of rudimentary capillary vessels and intercapillary endothelial cells with frequent cystic formations. These angioblastomas are neoplasms of mesoblastic elements in a neuroblastic structure; hence, they differ from the gliomas, in which there is also a new formation of vessels, but which are neoplasms of epiblastic, neural tissues with mesoblastic vascular accessory elements. In the angioblastomas the predominant factor is the capillary formation; the intravascular proliferation of endothelium is only a secondary feature. The latter may be predominant in some tumors, termed

81. Lotman, F.: Zur Kenntnis der Lindauscher Krankheit (des Centralnervensystem und der Retina), Schweiz. Arch. f. Neurol. u. Psychiat. **36**:257, 1935.

82. Collins, T. E.: Ocular Haemangiomatous Formations Associated with Vascular Tumors of Retina and Spinal Cord, Proc. Roy. Soc. Med. **24**:372, 1930.

hemangioendothelioma, whose differentiation from glioma may become extremely difficult. One of Collins' cases belonged to this group, as apparently did 1 of the cases of Brandt, in which the growth was somewhat more cellular than the capillary type.

In a later publication, von Hippel [83] similarly accepted the designation of hemangioblastoma. He examined an eye in which the temporal part of the retina was split into two layers and large and small cystic spaces occurred in its nasal part. The subretinal space was filled with coagulated fluid containing pigmented foam cells. In the angle of the retinal split proximal to the disk, a minute nodule composed of proliferating capillaries was noted. There were large vessels of the venous type with cuff-shaped infiltration of round cells, massively grouped pseudoxanthoma cells between the granular layers and necrosis of the retina with dissecting aneurysm of one of the large vessels. Ophthalmoscopic examination did not show any red or yellow nodule with the dilated pair of vessels; the angioblastic proliferation occurred only as minute nodules. Von Hippel formerly expressed doubt whether Emanuel's case belonged in the same group, but the similarity of his 2 last cases to Emanuel's was striking.

MacDonald and Lippincott,[84] whose patient was observed clinically by Scarlett [85] and Rhodes,[86] reported the histologic changes in one eye of a patient with bilateral angiomatosis of the retina. The condition, in their opinion, was a primary vascular growth with angioblastic derivatives, represented by cystic dilatations and capillaries, with secondary gliosis of long standing, which was likely to mask the true vascular derivation of the tumor. The larger part of the tumor was formed by a cellular glia matrix with a dense network of fibrils, smaller, waxy fibrils arising from one or both poles of the elongated cells. No definite arrangement of glial tissue—whorls of compact or loosely arranged forms, rosettes or palisading characteristic of neurogenic origin—could be detected. The slender, flat endothelial elements were occasionally closely packed. In the less dense areas ovoid cells with vesicular nuclei and few polygonal cells with central nuclei were seen. A few, and often degenerated, ganglion and mast cells with red granules in the cytoplasm were present. No pseudoxanthoma cells were noted, but in one part cholesterol crystals with foreign body giant cells were demonstrated.

83. von Hippel, E.: Angiomatosis retinae und Retinitis exsudativa Coats, Arch. f. Ophth. **127**:27, 1931.

84. MacDonald, R., and Lippincott, S. W.: Angiomatosis Retinae: Report of a Case with Pathological Study of the Enucleated Eye, Arch. Ophth. **20**:958 (Dec.) 1938.

85. Scarlett, H.: Angiomatosis of the Retina, Arch. Ophth. **54**:183 (March) 1925.

86. Rhodes, D. H.: Angiomatosis Retinae, Am. J. Ophth. **20**:522, 1937.

Koenig and Schoen [87] similarly accepted the view that the glial proliferation is only reactive, and not tumorous. Their tumor presented small nodules, and angiomatous parts were mixed with glial elements. In the meninges the large vessels were mostly of venous structure and were frequent in the angiomatous parts or connected with the angiomas. The fibrous thickening and hyalinization of the walls were considered secondary, the result of circulatory disturbance produced by the proliferating tumors. The same changes were described under different names, such as telangiectases, varices, angioma racemosum or angioma cirsoideum of the pial vessels. The presence of gliosis and syringomyelia with angiomatosis is viewed as a dysontogenetic disturbance; Lindau's disease is not exclusively a disturbance of the mesodermal part of the central nervous system, but is characterized by anomalies of the ectodermal part as well; angiomatous tumors and simultaneous vascular malformations are responsible for the occurrence of wide variations and overlapping pictures.

Grinker [88] described the tumor as hemangioblastoma, composed of convolutions of capillary size or wider (cavernous) spaces lined with actively proliferating endothelium, in which the connective tissue stroma is moderate and the thickened blood vessels are surrounded by glial proliferation, but the tumor should not be confused with and designated as glioma with involvement of the vascular elements. The angiomatous origin was similarly emphasized by Davenport, in whose experience the retinal tumors are highly cellular as compared with the tumors of the central nervous system. Stout and Murray [89] Zeitlin [90]; Wiedersheim [91] McGovern,[28] and Brain, Greenfield and Northfield [92] were unanimous in accepting the angioblastic nature as the fundamental feature of the growth. The last-named authors found in the retina of one eye two small, definite angioblastomas in the thinned and degenerated retina, where the outer granular layer disappeared and a great increase in the neuroglial fibers was noted, but the inner granular and ganglion

87. Koenig, E., and Schoen, H.: Diffuse Angiomatosis of Medulla and Spinal Cord with Syringomyelia (Lindau's Syndrome), Beitr. z. clin. Chir. **170**:239, 1939.

88. Grinker, R. R.: Tumors of Retina, Optic Nerve and Chorioid, in Ridley, R., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, 1940, p. 481.

89. Stout, A. P., and Murray, M. R.: Haemangiopericytoma: Vascular Tumor Featuring Zimmerman's Pericytes, Ann. Surg. **116**:26, 1942.

90. Zeitlin, H.: Haemangioblastomas of Meninges and Their Relation to Lindau's Disease, J. Neuropath. & Exper. Neurol. **1**:14, 1942.

91. Wiedersheim, O.: Ueber zwei seltene angiomatöse Veränderungen des Augenhintergrundes und über Erweiterung des Begriffes Angiomatosis retinae, Klin. Monatsbl. f. Augenh. **109**:205, 1942.

92. Brain, W. R.; Greenfield, J. G., and Northfield, D. W. C.: A Case of Atypical Lindau's Disease, J. Neurol. & Psychiat. **6**:32, 1934.

cell layers were distinguishable everywhere, except in the tumors. The tumors themselves consisted of a tangle of capillaries and many large, thin-walled vessels, 30 microns in diameter. The endothelial cells of the walls were swollen and possessed a granular cytoplasm. Within the tumor there were no neuroglial elements, although the overgrowth around the tumor was considerable and fibers penetrated the outer zones. Cystic spaces were present lateral to the tumor. Autopsy did not reveal any cerebellar cyst but showed typical hemangioblastomas of the spinal cord with cyst formation. The amount of collagen was in inverse proportion to the cellularity, and there were fewer foam cells than is usual in hemangioblastoma of the spinal cord. Syringomyelic cavities were lined by a thick layer of astrocytes, within fibers arranged concentrically in relation to the cavities. Tumors of the spinal cord and meninges were reported by Schuback[2]; Kernohan; Woltman and Adson; Davison, Brock and Dyke[93]; Koenig and Schoen,[87] and Craig, Wagener and Kernohan.[94] In 5 of these cases, hemangioblastoma of the cerebellum was present; in the other, that of Koenig and Schoen, as well as the case of Craig, Wagener and Kernohan, there were similar tumors of the fourth ventricle. In neither of these last-named cases were retinal tumors associated with the tumors of the central nervous system, but in 3 of the others, bilateral retinal tumors, and in a fourth, unilateral retinal tumors, were noted. In the case of Brain, Greenfield and Northfield, the changes were only in the spinal cord but were accompanied with unilateral multiple retinal tumors. The consensus is that the syringomyelia results from a separate developmental abnormality, and, not like the cerebellar cyst formation, from transudation of plasma from the tumor into the nervous system. The extension of the cavities, in the authors' case, up to the medulla, and their termination in the gray matter around the central canal, the location of the cavities in idiopathic syringobulbia, points to the validity of this explanation.

In the literature of recent years, only one dissenting note has been raised, that of Czukrasz,[95] who, following Meller and Marburg, stated that the neoplasm was of ectodermal origin, an angiogliosis, followed by secondary vascular changes. In her first case, in which the diagnosis was glioma, the retina had undergone complete disorganization as a result of a tumor, 2 mm. in width, behind the ora serrata. In her second case there was a worm-shaped mass between the retina and the

93. Davison, C.; Brock, S., and Dyke, C. G.: Retinal and Central Nervous Haemangioblastomatosis with Visceral Changes, Bull. Neurol. Inst. New York **5**: 72, 1936.

94. Craig, W. M.; Wagener, H. P., and Kernohan, J. W.: Lindau-von Hippel Disease: A Report of Four Cases, Arch. Neurol. & Psychiat. **46**:36 (July) 1941.

95. Czukrasz, I.: Angiomatosis Retinae with Report of Two Cases, Brit. J. Ophth. **21**:368, 1937.

choroid in the upper part of the globe; the tumor was growing to the temporal edge of the disk and extended in fan-shaped formation to the adjoining retina. The neural elements of the retina were displaced by neuroglial tissue and pseudoxanthoma cells. Mingled with the foamy structure of these cells was a considerable amount of pigment granules; in the center of the tumor cystic degeneration was evident. In the center of the tumor was a mass of isolated vessels, consisting mostly of capillaries, surrounded by pigment cells. The capillaries were present in the vitreous, adjacent to the retina. Czukrasz expressed the belief that the growth was hamartomatous in type, like the dysontogenetic tumors of the central nervous system, and ectodermal in origin, with the initiating cause located in the neuroepithelium. Probably the tumor starts from embryonal rests, growing and breaking the junction of neuroepithelial cells, a hypothesis which explains the presence of glial tissue, epithelial cells of embryonic character and the growth of the pigment epithelium. The presence of blood vessels was considered secondary. The correctness of the interpretation is attested to by the fact that both patients were children (respectively, 8 and 11 years of age), in whom hemangioblastoma is relatively infrequent, and that both cases represented a rather late stage, which is not ideal for differentiation and interpretation.

The histologic picture of this retinal tumor shows wide variations, due to individual reactive and inflammatory-degenerative changes. The eye as a rule is enucleated only at a late stage, many years after the original lesion has become established, and the subsequent detachment of the retina, the uveitis or the secondary glaucoma is a complicating or confusing factor in evaluation of the features. Hence, early enucleation of the eye is of paramount importance; in the case of multiple lesions the small, young nodules represent the true characteristics of the initial growth.

The tumor is intraretinal and is sharply defined in relation to the normal retina; it is composed of a network of vessels of very small caliber; the walls usually consist of a single-layered endothelial channel with a narrow connective tissue layer. The small vessels are often collapsed, do not exhibit a lumen or may be filled with red blood corpuscles. The vascular loops are often closely packed, coils touching coils without any interstitial tissue substance. Either glial tissue is absent in such parts, or only traces are detectable. In other instances the vascular loops are loosely arranged, with the interstitial substance more pronounced and with a glial network between the loops; the glial proliferation, through richness of cells, stains relatively darkly, and often the demarcation from the normal retina is less sharp. Keller gave ten characteristics of this tumor in the central nervous system: 1. It appears rich in cells under low magnification, and the high power lens discloses

small vessels and sprouting capillaries. 2. The endothelial lining varies; the larger the transverse section of the vessels, the flatter and darker are the endothelial cells. Capillaries with swollen endothelium and nuclei poor in chromatin, and capillaries filled with similarly constituted cells appear as hemangioendotheliomas. 3. Cells between the capillaries are responsible for the greater part of the tumor and differentiate it from the ordinary angioma; cells with large, light nuclei form a syncytial network. 4. Giant cells with nuclei rich in chromatin are encountered. 5. Xanthoma cells are numerous. 6. Cystic spaces of cavernous type with endothelial lining and a wall of fibrillar connective tissue continuing into the lamina choriocapillaris are observed. 7. Circulatory disturbance and accumulation of plasma in capillaries and tissues lead to cavity formation. 8. The periphery of the tumor shows vessels with characteristic normal walls. 9. The tumors are sharply outlined in relation to the normal constituents of the central nervous system. 10. Specific staining methods disclose a reticular network with delicate vessels and capillaries surrounded by cavities.

The lesions within the retina and in the central nervous system appear as a capillary angioma, a systemic disorder, probably related to, and rather like, cavernous angiomatosis; but the two conditions clearly differ, and, according to Lindau, their coincidental occurrence in the same family has never been observed. The initial intraretinal nodule expands and destroys either the external or the internal limiting membrane. The lumens of the capillaries may close and are replaced by solid stripes or plates. The glial elements between the loops of vessels either form a delicate fibrillary network or are more or less strongly developed, or, instead of glia, connective tissue may be found. The proliferating endothelial cells closing the lumens of the capillaries appear often to be breaking through the adventitia. Through intimal and adventitial proliferation, the muscularis and elastica disappear, making the differentiation of arteries and veins extremely difficult, even in sections. The adventitia of the larger vessels is often swollen. The affected entering vessels are thickened; cuff-shaped round cell infiltrations and endarteritic and endophlebitic changes are occasionally conspicuous. The growing mass of the tumor breaks through the retina in either direction; in the case of Collins the proliferation encroached on the cornea through the vitreous. The retina becomes adherent to the choroid at the site of the tumor, the connecting tissue showing hyaline or inflammatory characteristics. In the cases of long standing, ossification, with formation of marrow bone, has often been noted (Collins; Czermak; von Hippel; Gamper; Heine; Carr and Stallard; Brain, Greenfield and Northfield, and Talkowski[96]). The

96. Talkowski, S. I.: Nature of Hippel-Lindau Disease (Systemic Angiomatosis), Vestnik oftal. **15**:180, 1939.

assumption of Davison, Brock and Dyke that the ossification in their case was unique, and not encountered before, finds manifold contradiction in the cases of previous observers. Collins expressed the belief that the fibro-osteogenic membrane appears to be an effort on the part of the surrounding mesoblastic tissue to encapsulate the growth. In the absence of adhesions between the choroid and the retina, a wide separation of the retina is established; the subretinal fluid is rich in fibrin, with cholesterol crystals and remnants of proliferating pigment epithelium.

As a result of secondary changes in the retina, the disappearance of the cones and rods and the relatively conspicuous preservation of the inner layers, especially the ganglion cell layer, are the rule. Through proliferation of the layers the outlines become confused, and the proliferation, combined with multiple foldings, may produce a picture in which the retinal layers intermingle. In other cases the inner and outer layers do not form separate entities but are fused into a single layer. The parts of the retina adjacent to the tumor are thickened, edematous and vacuolar, with small cystic cavities or large cysts. In some cases glial proliferation, and in others connective tissue proliferation, within the retina is the rule. The pigment epithelium is either absent or shows a strong proliferative tendency; invasion of foam cells from the subretinal space takes place. The usual situation of the tumor at the periphery is responsible for the fact that the secondary changes diminish toward the disk.

The choroid is free of pathologic changes; it is sometimes atrophic but rarely thickened (cavernous in the case of von Hippel). The pigment epithelium is absent over long stretches or proliferates in masses and forms foam cells. The lamina vitrea is discontinous, especially at the site of adhesions; it is rarely the site of round cell infiltration (Czermak) and is the usual starting point of the fibrous tissue formation with ossification.

In the vitreous fibrinous exudate is not rare.

The characteristic constituents of the tumor are the convolutions of vessels with possible proliferation of glia and connective tissue elements. The portions of the tumor change from rich-celled to looser areas; the highly stained cells are often arranged in round groups surrounded by fibers, producing the impression that the tumor consists of endothelial elements. In tumors of the central nervous system silver staining often demonstrates an irregular net of reticular fibers, the delicate ones surrounding individual cells, the larger ones not penetrating between the cells but leaving larger nests of cells free. The cells may be rich or poor in chromatin; the nuclei may be polymorphic. According to Roussy and Oberling, the capillary walls are not formed of single layers of endothelium alone but contain pericytes with various types

of nuclei and are considered as part of the reticuloendothelial system. The sharp demarcation of the tumors from the normal tissue, the absence of mitotic figures and the similarity of structure in spite of the polymorphism of the nuclei constitute the benign characteristics of this tumor.

Next in importance to the typical convolution of vascular loops and the glial or mesenchymal interstitial cells are two features—the formation of cysts and the constant presence of pseudoxanthoma cells.

The cyst formation in the retina and in the central nervous system is due to circulatory disturbance, resulting in accumulation of fluid, not only in the tumor, but even in the adjacent normal tissues. In the cerebellum the cyst may be the size of a pigeon egg, with only a very small mural nodule in the wall. Experience has taught neurosurgeons that removal of the angiomatous nodule is of the utmost importance and that puncture of the cyst is of no avail, as the undiscovered and remaining angioma produces a new cyst through circulatory disturbance. According to Roussy and Oberling, the angioma possesses higher permeability than normal, leading to accumulation of lymph in the perivascular reticular spaces; for transportation of fluid there is hardly any provision. Furthermore, the xanthomatous changes in the reticulum, which differ greatly in the individual cases and become often the dominant feature, are the result of the circulatory disturbance characteristic of nerve tissues exclusively. The lymphostasis is responsible for the infiltration of lipid cells; in the retina the transportation of lymph depends on the pericytes. Keller pointed to circulatory disturbance in explanation of the cysts and called attention to the absence of necrosis. Schley emphasized the absence of any epithelial lining of the cysts; only rarely are there a few flat, endothelial-like cells, but these are not connected, and the contents, therefore, cannot be derived from the cystic wall. There is no apparent reason for assuming a secretory function for the cell-poor glial substance; consequently, the origin of the cysts must be attributed to transudation due to circulatory disturbance. Cushing and Bailey recognized the property of hemangiomas of exuding plasma and producing cysts with xanthochromic fluid. Sargent and Greenfield found the angiomatous cyst devoid of a lining membrane; the walls were formed by condensation of the normal neuroglia.

Formation of cystic spaces or large cysts is a constant feature of the retina, not only in the tumorous, but in the adjacent, parts. The smaller cysts may be confined to a single layer; the larger ones extend into more layers, but rarely into the neuroepithelium, owing to the resistance of the external limiting membrane. The cystic dilatations are sometimes empty, and sometimes filled with blood; usually their contents are similar to the subretinal transudate and with the Van Gieson stain show the characteristic pinkish color and homogeneous appearance. The

larger cysts are usually without any lining, owing to pressure from within or to degeneration. Niccoll and Moore found cavernous spaces lined with endothelial cells and filled with blood; MacDonald and Lippincott described large cystic dilatations either lined with endothelium or completely denuded of the lining cells. The mechanism of softening due to transudation in the production of cysts, postulated by Lindau, seems to be the correct one. Collins recognized cyst formation as due to active transudation of lymph from the vessels of the growth rather than to mere replacement by fluid of an area of degeneration.

Ginsberg and Spiro attributed the origin of xanthoma cells to the connective tissue, adventitia or glia cells. Leber compared foam cells to those encountered in exudative retinitis, but with a smaller amount of pigment. The cells have large nuclei with prominent chromatin; the size of the nucleus varies, being sometimes very large and sometimes small, irregular and pyknotic. Their origin from the pigment epithelium was not proved. Coats called them ghost cells derived from leukocytes; Marshall and Michaelson considered them histiocytes of the reticuloendothelial system. Jung studied the fat content of the tumors and found it to be mostly in the foam cells (pseudoxanthoma cells of Lindau) and to be without regressive changes, and therefore not degenerative. Lindau explained the fat content as being derived from the myelin of the medullated sheaths of the surrounding tissue, but their absence in the wall of the cysts, where myelin should be primarily present, and their presence within the retina, a tissue not carrying medullated fibers, contradicted Lindau's opinion. Lindau was compelled to modify his opinion and later explained the fat as a local xanthoma caused by transudation of plasma with high cholesterol content due to circulatory disturbances. Jung, similarly, expressed the opinion that the circulatory disturbance was insufficient, as the abundant fat content was shown to have occurred in his case in the small tumors lacking both regressive changes and circulatory disturbances, and fat constituent was absent in the large tumors, where these changes were demonstrated with ease. Therefore the presence of fat in these tumors is due either to primary disturbance of the lipid metabolism or to affinity of the interstitial cells for lipid.

Koenig and Schoen occasionally encountered swollen cells with a large amount of cytoplasm. The cells were visible not only in the interstitial tissue, but in the endothelial cells in the vessels. These cells gave a positive reaction with sudan III, proving the presence of lipids. The cells, arranged in closely packed groups, appeared as pseudoxanthoma cells. The lipids stored in the cells were masses of plasma absorbed by the endothelial cells, and the authors explained their origin according to the concept of Jung. The production of pseudoxanthoma cells is a specific characteristic of the mesenchymal elements, especially the endothelium, being dependent on local and general changes in the

lipid metabolism. On the other hand they are to be explained as purely regressive changes, without lipid involvement; however, Lindau pointed to their good staining quality, which was evidence against the degenerative nature of the process. Other investigators identified the pseudoxanthoma cells as neuroglial cells with an epithelial aspect. Cushing and Bailey proved that they contain a large amount of fat in the form of small droplets and that the dissolving of the fat during the embedding results in the honeycomb appearance. These authors could follow the transformation of endothelial cells of the capillary network into swollen, fat-laden intravascular cells. Zeitliń considered the possibility that the lipid content of the intravascular cells is due to reduced nutrition and fatty metamorphosis of the tumor cells as a result of circulatory disturbance, but, in view of the known phagocytic powers of the endothelial cells, he found the explanation insufficient. In his opinion, the lipids may be the product of the metabolism of the cells and are characteristic of these tumors; or, as Globus maintained, these cells may be the cleavage products in the formation of the primitive meninges. The pseudoxanthoma cells are constant elements of this tumor. Another constituent, the mast cell, is infrequent. Maspes described them; Jung encountered them constantly, and reexamination of Kufs's [97] slides proved their presence. Among the tumors of the brain, meningiomas, but not gliomas, are known to have mast cells. In the retinal hemangioma, their presence was noted by MacDonald and Lippincott.

COEXISTENCE OF TUMORS IN THE RETINA AND THE BRAIN

Up to 1912, the attention of observers was occupied solely by the clinical and pathologic manifestations of the retinal arteriovenous aneurysm, or capillary angioma. Seidel was the first to recognize and direct attention to the possible relation of this retinal lesion to neurologic symptoms of great variation and of hitherto unknown significance. In Seidel's case, representing the early stage of typical unilateral hemangioblastoma of the retina, bilateral choked disk was present, and operation revealed the presence of a cerebellar cyst. It was remarkable that the brother of the patient had no retinal involvement but was operated on for cerebellar cyst. Seidel mentioned this fact and pointed out that 3 similar observations had been made in the relatively scant literature prior to 1912. In Czermak's case autopsy revealed the presence of hydrocephalus, cystadenoma of both ovaries and a cerebellar cyst. In Jacoby's case the presence of postneuritic atrophy with a possible history of choked disk suggested intracranial complications, and in the case of

97. Kufs, H.: Beitrag zur Klinik, Histopathologie und Vererbungspathologie der von Hippel-Lindauschen Krankheit auf Grund der Untersuchung eines neuen Falles, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:414-427, 1932.

von Dzialowski such a complication was positively established. Leber [98] realized that postneuritic atrophy and choked disk are simultaneously present with, but are independent of, the hemangioma of the retina, indicating the presence of increased intracranial pressure; in his contention the cerebellar cyst and the retinal angioma are manifestations of a similar congenital anlage, and the familial occurrence of Seidel's cases proved the validity of his assumption.

Leber's deductions and Seidel's observations remained unsupported for many years, until Brandt published his autopsy observations on von Hippel's original patient, twenty-four years after the initial symptoms of the eye were observed and eight years after the enucleation of the involved eye. The patient exhibited cerebral symptoms (cerebral symptoms had previously been mentioned, without any further details, by Ginsberg and Spiro), and autopsy revealed multiple tumors in the central nervous system—at the base, in the cerebellum and in the cord—as well as in the kidneys, bladder, epididymis and bones, and numerous cysts in the pancreas and kidneys. Brandt reported a second case, that of a boy aged 12, who had vitreal and preretinal hemorrhages in one eye, with disk-sized retinal tumors in the lower nasal and upper temporal parts, respectively. In the course of the disease the tortuosity and dilatation of the vessels increased; later a new tumor appeared, followed by detachment of the retina; the patient died after the development of cerebral symptoms. Autopsy was not performed. Brandt considered the presence of multiple primary tumor formation without metastasis; he stated that the tumors of the central nervous system and abdominal organs are not related to the retinal tumors but are based on a similar developmental disturbance, an opinion which later formed the basis of Lindau's theory of mesenchymal disturbance.

In the case of Berblinger and Heine, autopsy revealed tumors of the central nervous system, with four pinhead-sized cysts, a cystic pancreas and renal cyst. In Lindau's case of hyperplastic capillary angioma, there was detachment of the retina in one eye and choked disk in the other; autopsy revealed hydrocephalus and a cerebellar cyst with mural nodule. In the second case of Lindau there was angiomatosis of the retina of one eye; the sister of the patient died of a cerebral tumor. Autopsy revealed angioma of the cerebellum and spinal cord with cyst formation, cystic pancreas, renal cysts and carcinoma (hypernephroma) of the kidneys and epididymis. In Rochat's case, one of retinal angioma in one eye and of choked disk in the other eye, cerebral symptoms developed; trephination was unsuccessful, and autopsy proved

98. Leber, T.: Erkrankungen der Netzhaut, in Graefe, A., and Saemisch, T. Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, W. Engelman, 1915, vol. 2, p. 1966.

the presence of cerebellar cyst with hyperplastic capillary angioma, and hydrocele with cyst formation in the epididymis. In the 2 cases of retinal angioma reported by Wohlwill and Schuback, autopsy furnished a similar picture—tumor of the roof of the fourth ventricle and spinal cord, syringomyelia, cystic pancreas, renal cysts and hypernephroma. Jess noted angioma of the retina, angiogliosis of the spinal cord with cysts, cystic pancreas and renal cysts. Cushing and Bailey removed at operation a hyperplastic capillary angioma with cerebellar cyst in a case in which retinal angiomatosis was diagnosed ophthalmoscopically. The number of similar observations on the coexistence of retinal tumor and tumors of the central nervous system and abdominal organs steadily increased; Knodel listed 16 among 61 cases with cerebral symptoms, or 25 per cent. The 16 cases included, in addition to the instance just noted, are those of Tresling, Aust, Rochat and Moeller.

In Tresling's[99] case 2 brothers had angiomatosis of the retina; the third brother had choked disk and epileptic fits, and tumor of the brain was diagnosed and trephination performed, without further light being shed on the nature of the cerebral involvement. The mother of the 3 brothers had died of a disease of the brain. Similarly, in the case of Aust, the presence of an intracranial lesion was suspected but not definitely proved; in this case, bilateral angiomatosis was complicated by choked disk, and a roentgenogram of the skull revealed increased intracranial pressure; a tumor of brain was suspected. These 2 cases are not definite, as was the case of Vossius, mentioned by Leber. In Rochat's case angiomatosis of the retina existed in 2 members of the family, and the third (the third brother of the second generation) had bilateral choked disk with tumors of the cerebellum and cerebrum disclosed at autopsy. In Moeller's case there was choked disk in one eye with a typical peripherally situated tumor in the other; in the lateral wall of the cerebellum a cherry-sized cyst was situated, which was diagnosed by Lindau as hyperplastic capillary angioma. In Knodel's case (that of the daughter of von Hippel's original patient) angioma of the retina was associated with cystic tumors and syringomyelia of the spinal cord, cysts of the right kidney, hemangioma of the adrenal gland and cystadenoma of the left kidney. In the case of Paton, Williamson and Noble there were advanced angioma of the retina of the right eye and early retinal angioma with choked disk in the left eye; the operation was performed one year after Lindau had shown the relation to cerebellar cyst, and his work was not yet familiar; consequently, instead of a subtentorial decompression, decompression was performed in the right occipital region, and the tumor therefore could not be

99. Tresling, J. H. A. T.: Ueber Angiomatosis retinae, Klin. Monatsbl. f. Augenh. **64**:306, 1920.

located; only a great excess of fluid presented in the subarachnoid space. Sladden found two tumors (one external to the cerebellum and one intracerebellar) in the central nervous system associated with two renal tumors in a patient who clinically had been observed twenty years earlier by Thomas and Coats to have a unilateral ocular lesion. The case of Oguchi [100] is hard to classify, as the clinical diagnosis was bilateral acute Coats's retinitis (retinitis exudativa) with cerebellopontile tumor; the histologic study revealed the dominance of the glial over the angiomatous elements in both the retinal and the cerebellar tumor. Oguchi made the diagnosis of polymorphous malignant glioma with meningeal infiltration, possibly with metastasis along the sheaths of the optic nerve, and he proposed the interpretation of Lindau's disease on a broader basis to include not only the angiomas of the retina and brain but the gliomatosis of these structures and the intermediate type of changes, retinitis exudativa (Coats's disease). Hartmann and Sourdille [101] observed a family in which the mother had choked disk and operation was successfully performed for a large angioma of the temporal lobe; the son had typical unilateral retinal angioma with a normal neurologic status. In the 7 cases of Jung there were cerebellar angiomas—in 6 cases with cyst formation and in 1 case angioma alone without cyst—and in 1 of the cases there was associated angioma of the retina (Lotman). In Marchesani's [102] case the unilateral retinal angioma was associated with cerebellar tumor. In Prevec's case of unilateral retinal angioma roentgenographic changes were interpreted as angioma of the spinal cord, but the diagnosis was not confirmed at operation. In Raney and Courville's [103] case of bilateral retinal angioma autopsy showed multiple angiomas of the cerebellum. MacDonald observed two families with coincidence of retinal and cerebellar angiomas. In the first family, one sister had unilateral retinal hemangioendothelioma, and a cerebellar hemangioma was removed at operation. The second sister had the same association of retinal and cerebellar hemangioendotheliomas. In the second family the father became blind at the age of 35 and died five years later of cerebral complications. The son was operated on for a midline cerebellar cyst, and the daughter had a similar operation for cerebellar

100. Oguchi, C. H.: Ueber eine Netzhauterkrankung, kombiniert mit Kleinhirntumor (sog. Lindau'sche oder von Hippel'sche Krankheit) und die Beziehungen zur Coats'schen Krankheit, Acta soc. ophth. Jap. **35**:1931; Klin. Monatsbl. f. Augenh. **88**:270, 1932.

101. Hartmann, E., and Sourdille, G.: Maladie de Lindau et angiome du cervelet chez la mère, maladie de von Hippel chez le fils, Ann. d'ocul. **168**:881, 1931.

102. Marchesani, O.: Ein Fall von Hippelscher Netzhauterkrankung mit operativ geheilter Kleinhirncyste, Klin. Monatsbl. f. Augenh. **94**:98, 1935.

103. Raney, R. B., and Courville, C. B.: Multiple Haemangioblastomas of the Central Nervous System, Bull. Los Angeles Neurol. Soc. **2**:104, 1937.

tumor of cystic type and was totally blind in both eyes as a result of bilateral detachment of the retina. In the discussion, Greenwood and Atkinson reported on a case in which the retinal hemangioma was associated with cerebellar cysts. In Koenig and Schoen's case bilateral choked disk, retinal bleedings and paralysis of the left superior rectus muscle represented the ocular complications; autopsy revealed hydrocephalus, multiple angiomas of the cord, central gliosis, syringomyelia, tumors in the floor of the fourth ventricle, numerous cysts in the kidneys, hypernephromas and cystic pancreas. In the family observed by Brukker,[104] several members exhibited angioma only of the retina; others, angioma only of the central nervous system, and some, a combination of the two. In the first generation only the cerebellar tumor was noted; in the second angioma of the retina and the coexistence of cerebellar tumors were noted; in the third generation 2 members had retinal tumors and a third had bilateral choked disk and underwent decompression for an inoperable massive cerebellar tumor. MacNab's [105] patient had angioma and detachment of the retina in one eye and choked disk in the other; operation revealed a large cerebellar cyst on the left side, with a small mural nodule protruding into the cavity; the tumor proved to be a hemangioblastoma, consisting of a mass of angiomatous vessels. The fifth case of Rumbauer, one of bilateral retinal angioma in which a previous operation had been performed for cystadenoma of the pancreas, resembled the case of Davison, Brock and Dyke, in which a patient with bilateral retinal angiomatosis had a pancreatic cyst removed, and that of Cahill, Melicow and Guerry,[106] in which the ocular findings consisted of optic nerve atrophy with bitemporal hemianopsia and a tumor removed from the kidney furnished the typical pathologic features of hemangioblastoma. The last-mentioned cases and the case of Knobloch testify to the interesting fact that the spreading knowledge of Lindau's correlation benefited not only neurosurgery, but abdominal and genitourinary surgery as well.

The simultaneous occurrence of hemangioblastoma in the retina and in the central nervous system seems to be assured, even if not definitely proved in some cases. Vogt and Meyer observed a family in which father and daughter had bilateral retinal angiomatosis; the paternal grandfather died of a cerebral tumor, verified at autopsy, but without a more accurate classification of the tumor. Knobloch's patient, a woman aged 38, for twenty-one years had suffered from plastic iridocyclitis and complicated cataract of the right eye, with typical changes in the

104. Brukker, J. J.: Angiomatosis retinae, Nederl. tijdschr. v. geenesk. **5**:28, 1938; Zentralbl. f. d. ges. Ophth. **43**:249, 1939.

105. MacNab, G. H.: Lindau's Disease, Proc. Roy. Soc. Med. **34**:324, 1941.

106. Cahill, G. F.; Melicow, M. M., and Guerry, DuP., III.: Renal Lesions in von Hippel-Lindau Disease, Am. A. Genito-Urin. Surg. **35**:271, 1943.

left eye—dilatation and tortuosity of the superior nasal artery and vein, leading to a gray-green, balloon-like retinal detachment, where the dilated vessels disappeared suddenly. The patient had had diabetes after operation for pancreatic cyst eight years previously. Her mother died after operation for brain tumor (allegedly glioma); one of the sisters died, similarly, of brain tumor and another after operation for cerebellar cyst. In the first case of Talkowski (both cases were of bilateral angiomatosis of the retina, in 2 women aged 26 and 28, respectively) the patient had unilateral headaches and noise in the ear and exhibited Oppenheim's sign and increased reflexes on the right side, suggesting central angiomatosis. In the second case headaches, nausea, vomiting and convulsions of the body and extremities pointed to possible involvement of the rhomboid area of the brain. In the fourth case of Smelanski, that of a man aged 33, there was unilateral retinal involvement, complicated by debility and cerebellar ataxia, and in his fifth case (that of a woman aged 39), of bilateral retinal angiomatosis, the patient exhibited epileptic seizures and suffered from headaches, and the neurologic examination postulated organic changes in the left cerebellar hemisphere. The cases enumerated in the last group did not furnish factual evidence of the systemic involvement in association with the retinal disease. On the other hand, the recent paper of Moeller, revising the dates of his previously published observations, contains information of paramount significance. Moeller mentioned that of 27 cases of angioreticuloma treated surgically, paralysis of the sixth nerve was present in 6 (in 1 case bilaterally) and choked disk in 20. Three of the 27 patients operated on for hemangioma belonged to Lindau's original family, observed and described in 1929. Five members of the family had solely cerebellar, 1 retinal and 3 a combination of cerebellar and retinal angiomatosis. Craig, Wagener and Kernohan observed the association of retinal angioma with hemangioblastoma of the cerebellum in 4 instances, all verified by operation and autopsy. In 3 cases a cyst was associated with an angiomatous tumor; in the fourth case a small cyst was present at the upper pole of the neoplasm. In 1 case the onset and development of the retinal lesion were uncertain; in another the lesion was unilateral, and in the remaining 2 cases it was bilateral. In 1 of their cases the mother of the patient died at the age of 48, having been blind in one eye for several years and having suffered from pain in the neck and paralysis of both arms for six months before death. An older brother of the patient died of brain tumor; a younger sister had angioma of the retina and died at the age of 18, after suffering from pain in the neck for six months. In the last case, one of a bilateral retinal lesion, the operation exposed a large hemangioma which filled the fourth ventricle and posterior cistern and involved the pons, the medulla oblongata and the upper cervical portion of the spinal cord. Necropsy

revealed the presence of another tumor in the right hemisphere of the cerebellum, syringobulbia, syringomyelia, a tumor in the lumbar region of the cord, cysts of the pancreas and kidneys and adenomas of the kidneys and epididymis.

It has already been mentioned that in the case of Brain, Greenfield and Northfield and in that of Bockoven and Levatin, the retinal lesion was associated with tumors of the cord only, and in others the tumor of the spinal cord was only part of the involvement of the central nervous system.

GENETIC BACKGROUND

The hereditary nature of the retinal lesion was long unsuspected. Similarly, inheritance of the tumor in the brain was not considered; Bruns [107] stated recently that it had not been observed and that in his opinion, even if such an occurrence should be noted in the future it would represent only a peculiar coincidence. With regard to the retinal lesion, Collins described the clinical picture and recognized pathologically the presence of capillary nevus and the horizontal inheritance in 2 members of the same sibship, without, however, stressing the point of inheritance. Fifteen years later, Griffith and Ormond published the pedigree of 2 sisters, involving 3 eyes (2 examined pathologically and 1 clinically) with intraocular angioid growth but raised the question whether there was a general disease of the terminal branches of the retinal vessels supplying the outer retinal layer, and whether the ophthalmoscopic changes, such as massive exudation and vascular dilatation, were results secondary to long-standing capillary disease. The observation of Frenkel is of doubtful value, as the brother and sister were said to have angiomatosis of the retina but only the brother was examined; only in the history was it noted that the sister became blind at the age of 18 (no examination or further data were available). Tresling [99] and Rochat [108] independently reported on the same pedigree. Tresling reported the cases of 2 brothers with unilateral retinal lesion (multiple in one and a single nodule in the other) whose mother died of disease of the brain. A third brother had epileptic fits and bilateral choked disk; because of the diagnosis of tumor of the brain, trephining was performed, without further light being shed on the nature of the cerebral involvement. Rochat followed the fate of this family and found that the condition of the first and the third brother did not change. But the second brother, with angiomatosis of the retina, had detachment of the retina of the same eye, choked disk in the other eye and symptoms

107. Bruns, L.: Die Geschwülste des Nervensystems, Berlin, S. Karger, 1908.

108. Rochat, G. F.: Augenkrankheiten als Teil erblichen familiären Systemkrankheiten, Geneesk. tijdschr. v. Nederl.-Indië, 1939, p. 771; Zentralbl. f. d. ges. Ophth. **43**:587, 1939.

of cerebral tumor; autopsy proved the presence of cerebellar cyst. A brother and a sister in the second generation were unaffected. The third generation consisted of 1 normal child (10 months old) of the oldest brother, with angiomatosis of the retina, and of 7 normal children of the second brother, with angiomatosis of the retina (who died of angioma of the cerebellum); the third brother, with cerebellar tumor, had no children; the fourth, the unaffected brother, had 1 normal child, and the fifth member of the second generation, the unaffected sister, had 8 children, and her oldest son, 16 years of age, had bilateral retinal angiomatosis. The right eye showed retinal detachment with a red mass in the upper periphery; in the left eye, was a typical peripheral nodule.

The Rochat pedigree was the first to demonstrate horizontal and vertical inheritance in three generations, and the fact that in the third generation the son of the unaffected mother had a bilateral retinal lesion is of interest. Years later Rochat completed the family history as far as the third brother of the second generation, who had bilateral choked disk without angiomatosis of the retina; when the patient died, autopsy disclosed cerebellar and cerebral tumors of similar structure.

The observations of von Hippel, Brandt, Knodel and Seidel represent different members of the same family, the pedigree consisting of father, son and daughter with angiomatosis of the retina. The father, von Hippel's original patient, died of intracranial symptoms, in addition to tumor of the retina; tumors were present in the cerebellum, in the petrous portion of the left temporal bone, the cauda equina, both kidneys and the spleen. Brandt described the case of the son, and Knodel and Seidel, independently, the case of the daughter, who had, in addition, a cerebellar tumor (autopsy study by Knodel).

Polack and Frogé[109] reported on a mother and 2 daughters with atypical retinitis of two types. One type, common to the 3 patients, consisted of elevated white masses in the retina, covered in places by a firm vascular network. The second type, absent in the younger daughter, was a conspicuously raised mass, related to the white plaques and retinal exudation. The description of the authors is not that of the typical picture, but Baillart examined 1 of the patients and diagnosed the condition as angiomatosis of the retina; hence the familial occurrence is significant. In Lindau's second case autopsy showed angioma of the cerebellum and medulla oblongata, cyst of the pancreas, kidneys and epididymis, and a small capillary angioma of the retina of the left eye; in the case of the sister a diagnosis of cerebral tumor with choked disk (no autopsy) was made. In the case of Cushing

109. Polack, and Frogé; Rétinite atypique chez trois mémbres de la même famille, Bull. Soc. d'ophth. de Paris **33**:44, 1921.

and Bailey, that of cerebellar tumor with retinal angioma, the father died of rupture of a cystic tumor of the brain and an aunt died in similar circumstances of ruptured cystic sarcoma. Meller and Marburg's patient had a unilateral retinal lesion, bilateral choked disk and a cystic growth in the cerebellum with a mural nodule, diagnosed as glioma cysticum; but the exact nature of the tumor was not established because the specimen was lost; the patient's father died of cerebellar tumor.

Moeller [110] claimed simple dominant inheritance of a single factor, not sex linked, in the family tree he studied, the largest one observed. The father of the family died of brain tumor (probably capillary angioma); he had 5 living sons; 2 daughters died in early childhood. Of the 5 sons, 3 were affected, and the oldest affected son had 3 daughters, the first and the third being affected. The second affected daughter of the third generation had 1 affected daughter (6 years old at the time of the report). The oldest brother of the second generation died of cerebellar tumor (probably capillary angioma); the second brother, who was not affected, had 1 affected child. The third brother, who was affected and died at the age of 47, had 8 healthy children. Autopsy showed primary carcinoma of the adrenal gland with metastasis in the cerebellum. The patient was blind in both eyes; one eye was enucleated, but angioma of the retina was not diagnosed, either clinically or pathologically. In the author's opinion, the diagnosis was in error; he considered that there was angiomatosis of the retina, leading to secondary glaucoma; similarly, he considered the pathologic report mistaken and stated that it was highly probable that cystic hemangioendothelioma of the brain and adrenal tumor of identical nature were present. The fourth brother was healthy, and the fifth brother (the third one affected) was the original patient; he had choked disk in the right eye and a typical angiomatous nodule in the periphery of the retina of the left eye. Operation disclosed a cystic hemangioma of the right cerebellar hemisphere the size of a cherry. In the third generation, the oldest sister died at the age of 28 with symptoms of brain tumor and without ocular involvement; there was only suspicion, no evidence, of cerebellar lesion or tumor. The youngest daughter died at the age of 24; she had choked disk and verified capillary angioma of the cerebellum. The slides were seen by Lindau, and the tumor was diagnosed as such. The third of the sisters of the same sibship was not affected. Fifteen years later Moeller [111] brought additional data on the same family which revealed extraordi-

110. Moeller, H. U.: Familial Angiomatosis retinae et cerebelli—Lindau's Disease, Acta. ophth. **7**:224, 1929.

111. Moeller, A. V.: Ophthalmic Symptoms and Heredity in Cerebellar Angioreticuloma, Acta psychiat. et neurol. **19**:275, 1944.

nary penetrance. By that time the family tree included four generations, with 6 males and 4 females affected in three generations. Five of the members had cerebellar angioma; 3, cerebellar and retinal angioma, and 1, only retinal angioma, the character of the progenitor's cerebellar disease remaining uncertain. In a second family reported by Moeller, a mother and daughter were operated on for angioma of the roof of the fourth ventricle.

Collier [112] observed 2 sisters with capillary hemangioma not involving the eyes, the lesion being of the cerebellum in the one and of the spinal cord in the other; both had hypernephromas. Mawas mentioned two pedigrees of angiomatosis retinae without giving particulars on the relatives; in the first pedigree the brother and sister, and in the second the mother and 3 daughters, were affected. In Seidel's case 2 brothers had cerebellar tumor, and 1 of them had, in addition, angiomatosis of the retina. The patient of Hartmann and Sourdille had typical unilateral angiomatosis of the retina with normal neurologic findings; the mother had choked disk with a large cerebellar angioma (removed by operation), and the maternal grandfather died with symptoms of cerebral tumor. Martin and von Bogaert [113] described the cases of 2 sisters with clinical symptoms of brain tumor who died without operative intervention; in 1 patient autopsy revealed a typical cerebellar angioma, apparently without retinal lesion. Similarly, Vincent and Rappaport [114] observed cerebellar haemangioma in 2 members of the same family.

In the case of Lotman (ocular tumor) and of Jung (general involvement) there is the possibility of a hereditary factor, as the maternal grandfather died of brain tumor. Pana [115] described hemangioma in 2 brothers (no ocular lesion); in the case of Wolf and Willens [116] both eyes were enucleated for detached retina with secondary glaucoma (no clinical or pathologic details), but autposy revealed hemangiomas of the cerebellum and spinal cord, syringomyelia and syringobulbia, congenital cysts of the pancreas and kidneys and hypernephroma of the left kidney. The father died of brain tumor (no details), suggesting vertical inheritance in this pedigree. Karasek's [117] case of unilateral angiomatosis of the retina cannot be accepted as showing inheritance

112. Collier, W. T.: Two Cases of Lindau's Disease, Brit. M. J. **2**:144, 1931.

113. Martin, P., and von Bogaert, G.: Deux cas d'hémangiome du cervelet chez deux sœurs, J. belge de neurol. et de psychiat. **33**:809, 1933.

114. Vincent, C., and Rappaport, F.: Deux cas d'hémangioblastome du cervelet dont l'un familial, Rev. neurol. **1**:32, 1931.

115. Pana, C.: Su la morfologia e la istogenesi degli angioreticulomi encefalici (Morbo di Lindau in due fratelli), Riv. di pat. nerv. **44**:1, 1934.

116. Wolf, A., and Willens, S.: Multiple Haemangioblastomas of Spinal Cord with Syringomyelia: A Case of Lindau's Disease, Am. J. Path. **10**:545, 1934.

117. Karasek, O.: Angiomatosis retinae (von Hippel-Lindau), Klin. Monatsbl. f. Augenh. **95**:163, 1935.

of the lesion; the mother and grandmother were blind, owing to glaucoma, but nothing definite in relation to angiomatosis was proved in their cases. Marchesani's case belonged in the same category as Karasek's. Unilateral multiple tumor of the disk was associated with cerebellar tumor; the grandfather died of a lesion of the brain; the sister of the patient was mentally abnormal, but angiomatosis was not proved as a vertically inherited lesion.

In the case of Levin [118] there was capillary hemangioblastoma of the dorsal surface of the first cervical segment of the spinal cord with cyst of the cerebellum. The father of the patient had cerebellar hemangioblastoma, showing intermittent intracranial pressure, paucity of signs of cerebellar involvement and occasional ipsilateral astereognosis; an aunt had less definite symptoms; nevertheless, the symptoms were indicative of intracranial tumor rather than of any other disease.

The family tree published by Vogt and Meyer is the third important pedigree, in significance next to those of Rochat and Moeller. Vogt and Meyer observed bilateral retinal lesions in father and daughter; an other daughter was normal, and the fourth child (a son) had a unilateral patch, apparently in the choroid, without any possible relation to the angiomatosis of the father and sister. The paternal grandfather died of brain tumor, which was verified at autopsy, without accurate classification of the tumor. The family tree revealed vertical inheritance in two, and possibly in three, generations, if the grandfather's unclassified cerebral tumor is accepted as belonging to the same group. Furthermore, one need not disregard the rare clinical characteristics; in his case the retinal lesion not only did not progress, but was even subjectively improved at the age of 56. This slow progression was occasionally noted by other observers but is rather rare.

In the pedigree observed by Iles [119] the mother died of stroke, and autopsy was not done. Her brother had a cerebellar cyst, verified at operation. In the second generation there were 4 children. Of these 4 siblings, the oldest, a boy, died of cyst of the brain; the second, a girl, died of stroke; the third child, a boy, has hemangioblastoma of the retina, and the fourth child, a boy, has a typical unilateral retinal lesion, without involvement of the central nervous system. In the collateral line of the family, a nephew died of retinal hemangioblastoma, and an aunt had cysts of the breasts and an abdominal disorder suggesting cysts of the kidney.

The multiplicity of the lesion within the same family also appeared in the pedigree reported by Brukker. The mother died of cerebellar

118. Levin, P. M.: Multiple Hereditary Haemangioblastomas of the Nervous System, Arch. Neurol. & Psychiat. **36**:384 (April) 1937.

119. Iles, A. E.: Von Hippel–Lindau's Disease, Proc. Roy. Soc. Med. **32**:1618, 1939.

tumor; of her 6 children, 1 died accidentally at an early age, another disappeared. Three of the sons died at an early age of angiomatosis of the central nervous system. Two of the 3 brothers had unilateral retinal angiomatosis. The unaffected daughter married, and 3 of her 8 children were affected. The oldest son had bilateral retinal lesion; his right eye was enucleated, and examination proved the presence of retinal angiomatosis. The fourth son had angiomatosis of the retina of the right eye. The daughter had bilateral choked disk, and a decompression was done because of an inoperable massive cerebellar tumor. In Knobloch's case the right eye was blind as a result of plastic iridocyclitis and complicated cataract; the left eye showed angiomatosis with detached retina; the patient had had diabetes after operation for pancreatic cyst eight years previously. Her mother died after an operation for brain tumor (allegedly, glioma); 1 of the sisters died after an operation for cerebellar cyst, and another sister died, similarly, of cerebral tumor. MacDonald [120] had the opportunity to observe two families and stated that in two generations of each family 6 members altogether were affected; actually, only 4 persons were affected among 11 members. In the first pedigree there were 2 affected sisters. The first sister had unilateral retinal lesion, detached retina, complicated cataract and secondary glaucoma. The retinal tumor, which was diagnosed as hemangioendothelioma, consisted of small vessels with single layers of endothelium, numerous partly formed vessels and large vessels surrounded by connective tissue; large endothelium-lined cysts lay close to the tumor. A cerebral hemangioendothelioma was removed surgically. The sister of the patient also had a lesion of the retina of the right eye, and operation was done for cerebellar hemangioma of cystic type. The mother of the sisters was blind in one eye after measles. According to the history, she died after operation for brain tumor; but the hospital records did not verify this statement, and the enucleated eye did not reveal changes characteristic of this type. Therefore, only horizontal inheritance was *de facto* present, the vertical inheritance (case of the mother) remaining highly uncertain. In the second pedigree of MacDonald the conditions were almost identical. The brother was operated on for cerebellar cyst; the sister, whose total blindness was due to bilateral retinal detachment, had an operation for cerebellar tumor of cystic type. The father of the patients became blind at the age of 35 and died at the age of 40 of cerebral complications, but no records were available to ascertain the type of lesion in his case.

Koenig and Schoen reported the data on two successive generations without involvement of the eyes, but with lesions of the brain in 2

120. MacDonald, A. E.: Lindau's Disease: Report of Six Cases with Surgical Verification in Four Living Patients, Arch. Ophth. **23**:564 (March) 1940.

members and symptoms in other members so typical that it is possible to include them as affected. In the first generation the father died after a decompression for tumor of the brain (choked disk and retinal hemorrhages were present in the right eye). He had 2 brothers and 1 sister. One brother was healthy and had no children; the second brother died young, and a sister, who had headaches and vomiting, also died. One of her daughters died young in similar circumstances. The patient, who was the son of the man who died of brain tumor, had bilateral choked disk, retinal hemorrhages, diplopia and proved typical involvement of the central nervous system and abdominal organs. In the second generation, a sister, 12 years of age, died with similar symptoms; a brother at the age of 19 had a cyst with a transparent membrane in the medulla oblongata.

Staz [121] reported a family consisting of the mother and 3 children with retinal lesions only (6 eyes affected). The mother's left eye was blind owing to iris bombé; the right eye showed massive exudation in the retina (Coats's disease), enormously distended veins (one of the veins disappearing into an angioma) and, beyond the angioma, an area of dilated capillaries. The right eye of one of the daughters had detached retina with two areas of capillary nevi and widely scattered areas of chorioretinitis, with massive retinal exudation and highly refractile crystals within; later an early angioma developed in the left eye. The older boy had a unilateral, pear-shaped angioma in the extreme periphery of the eye; the second boy also had a typical retinal lesion in one eye. In the pedigree reported by Rumbauer the eyes were predominantly involved. The family consisted of 5 affected members—3 brothers, their mother and the mother's sister. In the first case the retinal lesion was bilateral. In the right eye there was only an abnormal vein anastomosing with an artery; this led to the formation of multiple nodules fourteen months later, when marked angiomatosis of the left eye developed. In the second case the right eye was enucleated, and the left presented two large and numerous small nodules in the retina. In the third case the retinal lesion was similarly bilateral, with a small solitary angioma with typical vessels. The fourth case was the only one in which the retinal lesion was unilateral. In the fifth case the retinal involvement was, again, bilateral and an operation had previously been performed for cystadenoma of the pancreas.

Of the family of 5 members reported on by Smelanski, the father and daughter had typical unilateral angiomatosis; no information on the rest of the family was furnished. The mother of McGovern's patient with a retinal lesion died of an unidentified cerebral neoplasm; the

121. Staz, L.: Angiomatosis Retinae with a Report of Four Cases in One Family Involving Six Eyes, Brit. J. Ophth. **25**:167, 1941.

brother of the patient died of a cerebral lesion, diagnosed at operation as arteriovenous aneurysm of the cerebellum, and exhibited dilatation of the retinal vessels, choked disk and proliferating retinosis. Grossman and Kesert's [122] pedigree uncovered important data on the hereditary taint without participation of the eyes. The father was operated on for large cerebellar cysts with a tumor nodule, and microscopic studies revealed hemangioblastoma. Of his 4 children, 3 were affected. One daughter died suddenly at the age of 24 of probable cerebellar tumor; the first son was operated on for a tumor similar to father's. The other son had bilateral choked disk and nystagmus, and a diagnosis of cerebellar tumor was made. At operation the dura over the cerebellum was noted to be under great pressure, making removal of the tumor impossible. Therefore 1 member of the first generation and 3 members of the second generation had a tumor of the brain. In 2 members the presence of cerebellar hemangioblastoma was verified; in the other 2 the neoplasm was not determined, but in 1 of them cerebellar tumor was present but could not be removed at the operation. Brain, Greenfield and Northfield observed bilateral retinal hemangioma accompanied with tumors and cyst formation in the spinal cord and multiple cyst formation of the pancreas and kidneys. With respect to the possible hereditary tendency, the authors noted that 4 of the relatives had progressive visual disturbances, and another, intracranial tumor. Three of the members with ocular disturbances were noted only as blind, and the fourth was stated to have retinitis. In none of these 4 cases nor in the fifth case, one of intracranial tumor, were further details given on the pathologic changes; consequently, the hereditary involvement must be regarded as unproved.

In summary of the data on the hereditary factor of the disease, it is evident that horizontal, vertical, horizontal-vertical and collateral involvement occur. Horizontal involvement of the eyes only was reported by Collins, Griffith and Ormond, and Mawas (first case), horizontal involvement of the central nervous system only, by Collier, Vincent and Rappaport, Martin and von Bogaert, and Pana. Seidel, Lindau, McGovern, Knobloch and MacDonald demonstrated the horizontal inheritance of the equivalents of the disease, namely, the occurrence of retinal and cerebellar hemangioblastomas within the same sibship as the various manifestations of the hereditary trait.

The hereditary involvement in the vertical direction was demonstrated in a much larger group than the horizontal inheritance. Vertical inheritance of the ocular affliction without horizontal inheritance was present in the case of Smelanski. The pedigrees of Polack and Frogé,

122. Grossman, M. O., and Kesert, B. H.: Familial Incidence of Tumors of the Brain, Arch. Neurol. & Psychiat. **52**:327 (Oct.) 1944.

Mawas (second case), Staz and Rumbauer demonstrated horizontal and vertical inheritance involving only the eyes; on the other hand, the same hereditary trait was present but manifested itself only in the central nervous system in the observations of Levin, Koenig and Schoen, Grossman and Kesert, and Moeller (second pedigree).

The largest group of pedigrees revealed horizontal and vertical inheritance in families in which the members were afflicted either with manifestations of the eyes or with those of the central nervous system or with both simultaneously. In the last category belong the observations of Tresling, Rochat, Brandt, Meller and Marburg, Cushing and Bailey, Hartmann and Sourdille, Wolf and Willens, Moeller, Jung, Lotman, Vogt and Meyer, Iles, Brukker, and Lundsgaard.[123] In the last case angiomatosis of the retina was associated with an operatively healed cerebellar tumor; 2 brothers and 2 daughters of one of the brothers died of cerebral tumor.

The inheritance is doubtlessly a pleiotropic monogenic dominant variety affecting the tissues of mesodermal origin. The presence of the overt form in large numbers in successive generations proves the dominant character of the inheritance. The gene is autosomal, no sex linkage being present in the different pedigrees. In the majority of cases, except in the pedigrees of Rochat's and Brukker's, the dominance appeared as regular; in the pedigrees reported by these authors the transmission was an irregular or incompletely dominant type. The regular dominance appears in each new generation in a largely stable and identical phenotypical form, and the descendants of the unaffected member remain free of the disease. The irregular dominance is explained by nonpenetrance, the disease not becoming manifest, although the transmitting character was present in the germ plasm, as demonstrated by its transmission to the next generation. Particular genes show a characteristic percentage of penetrance; for instance, the blood groups always show 100 per cent penetrance; others, much less. In Rochat's and Brukker's cases the unaffected female transmitted the disease to the next generation. The irregular dominance explains satisfactorily this occurrence even if the transmitter was normal. However, the phenotypical form of the disease varies greatly among members of the same family, and the expression of the gene in a given case may be of so slight a degree that the individual member is considered as clinically unaffected and the dominance as undetected. The retinal angioma may be missed by ophthalmoscopic examination (as in the case of Lindau); the capillary angioma of the cerebellum may remain undiscovered before the cyst formation leads to pronounced clinical symptoms, and the

123. Lundsgaard, K. K. K.: Discussion of Capillary Angiomatosis, Internat. Ophth. Cong. **2**:634, 1929.

changes of the abdominal organs do not cause clinical manifestations in most cases; or the symptoms may develop only many years later, and therefore the dominant transmission remains undetected. Or, as in the pedigree of Vogt and Meyer, only involvement of the daughter's second eye led to the discovery that the father had a bilateral retinal lesion, and only on reexamination of the original slides of the first eye, which was enucleated, with a diagnosis of glioma, was the diagnosis corrected to angioma. Therefore, the apparent irregular dominance may be based either on actual nonpenetrance of the gene or, possibly, on nonrecognition of the phenotype, due to the complex nature of the syndrome. It is interesting to note that tuberous sclerosis and neurofibromatosis (Recklinghausen's disease), other forms of ectomesodermal blastomatosis, similarly show a dominant type of transmission.

Lindau noted that 20 per cent of the cases show a familial occurrence, and Usher [124] compiled 119 cases from the literature, with 22 cases occurring in 8 pedigrees and, with no record of any relative's being similarly affected in the remaining 97 cases. The known pedigrees testify to dominant transmission, and therefore, the remaining isolated cases are explainable only through new mutations of the gene, from normal to defective, producing sudden and discontinuous change. The mutations in general are often trivial in their effects, but often lethal or retrograde, hindering rather than helping the organism. The mutant gene reproduces itself, and hence it is transmitted, usually as a recessive character. Mutations occur constantly in nature, replacing the eliminated genes and keeping the hereditary diseases in the population at about a constant level. Reliable statistical data show that the incidence of hereditary diseases remains stable. From the standpoint of the present study, it would be important to follow up the descendants in the isolated cases to prove that the mutation which once occurred and produced the disease is discernible in their descendants in similar form and location.

DIFFERENTIATION OF ANGIOMATOSIS RETINAE AND RETINITIS EXUDATIVA (COATS'S DISEASE)

The differentiation of capillary angioma of the retina, clinically and pathologically, and its recognition as a distinct disease entity, required time and the minute observation of many workers. One cannot be surprised that in the early period, the criteria of differentiation not being sharp, the entity was often confused with similar conditions, especially with Coats's retinitis exudativa. The recognition that angiomatosis of the retina is the manifestation of the systemic involvement of the eye, the

124. Usher, C. A.: On a Few Hereditary Eye Affections, Tr. Ophth. Soc. U. Kingdom **55**:164, 1935.

work of Lindau, came at a comparatively late date, in 1926. Before Lindau's fundamental contribution, the confusion of angiomatosis of the retina with Coats's retinitis was not exceptional; but even after Lindau's concept became more widely recognized there were still observers who either failed to recognize, or did not accept, the sharp division between the two distinct entities.

Coats [125] in his first paper reported the pathologic examination in 6 cases and collected 48 cases from the literature with certain features in common; he divided the cases into three groups: (1) cases without gross vascular disease (2 of his own and 22 or 23 from the literature); (2) cases with vascular involvement (4 of his own and 7 from the literature); (3) cases with arteriovenous communication (18 from the literature). The condition occurred as a unilateral lesion. It has since been learned that occasionally it appears bilaterally (as in the cases of Lawford, Weinstein [126] and the fourth case of Zinsser [127]) in young persons of perfect health and no family history of a similar condition, being more frequently in males. Ophthalmoscopically, the presence of large masses of white or yellow exudate beneath the retinal vessels is the common feature; hemorrhages and cholesterol crystals are usually present. The choroid is practically intact. Organization and cicatricial contraction, crumpling and increasing detachment of the retina follow. Destruction or proliferation of pigment epithelium leads to lining on both sides of the space between the choroid and the retina; or, by penetration of the connective tissue mass, epithelial tubes, solid islands of pigment epithelium cells or a mass divided by blood vessels is formed. The nonessential vascular changes are dilatation with neglible changes in the walls, or thickening and hyaline degeneration of the walls, or a collection of cells of inflammatory nature within the walls or in the perivascular lymph spaces. The evidence from an early case, and from an additional 4 cases in his second publication [128] led him to the conclusion that the essential features are present as hemorrhages in the outer reticular layer of the retina and in the subretinal space, and that in hemorrhages in the latter area the breaking down results in formation of debris, fibrin and cholesterol and in the irritation leading to formation of granulation tissue and encapsulation. The exudate in the retina may present single or multiple patches, mostly at the posterior pole (only

125. Coats, G.: Forms of Retinal Disease with Massive Exudation, Roy. London Ophth. Hosp. Rep. **17**:440, 1908.

126. Weinstein: Ein eigentümliches ophthalmologisches Bild, Klin. Monatsbl. f. Augenheilk **45**:471, 1907.

127. Zinsser, F.: Beitrag zur Kenntnis der exsudativen Netzhauterkrankungen, Arch. f. Ophth. **121**:686, 1929.

128. Coats, G.: Retinitis exudativa (Retinitis haemorrhagica externa), Arch. f. Ophth. **81**:275, 1912.

exceptionally at the periphery, as in the case of Laval[129]), close to the disk or macula, or it may resemble that in retinitis circinata or exhibit tongue-shaped projections toward the periphery. In the early stages the exudate is loose and rich in cells. Deposits of lime and ossifications occur, especially if the choroid is affected. Between the retina and the choroid a mass of connective tissue forms; exudation on the external retinal surface with cystic degeneration of the retina and degenerated leukocytes appears, followed by infiltration of the choroid and formation of adhesions. Detachment and degeneration of the retina and hemorrhages into the vitreous are frequent complications.

According to Coats, the primary changes are hemorrhages in the external layers of the retina and in the subretinal space. The capillary hemorrhages in the outer reticular layer cause bulging of the external limiting membrane or rupture into the subretinal space; the decomposition of the blood-liberated toxins leads to an inflammatory reaction. The detachment of the retina, the inflammation of the choroid, the proliferation of the pigment epithelium and the increase of detachment due to the shrinking of scars are consecutive changes. The primary feature is represented by the hemorrhages, due to an abnormal constitution of the blood, either in the sense of change in coagulability or in local vascular changes; but Coats expressed the exudative or inflammatory nature of the condition by the designation of exudative retinitis. The vascular changes, if present, affect the branches of the second and third grade only, but are often clinically absent, and are not necessarily forerunners of the disease. The vascular changes usually affect the veins and vary from dilatation, with slight changes of the walls, to thrombosis, accumulation of leukocytes in and around the walls, thickening and hyaline degeneration, endothelial proliferation and, finally, poor staining and fragmentation of the nuclei and a fibrous appearance of the walls. The vascular changes and exudation do not correspond in their distribution; exudation occurs without vascular changes at the site of the exudation, or the vascular changes are missed altogether. The absence of vascular changes points to the possibility of their being a secondary feature due to shrinking or closure or to toxins, but the assumption of vascular changes would furnish the easiest explanation.

Coats included only the first two of his groups in the retinal disease of massive exudation and mentioned the third, with arteriovenous communication, as resembling the second group; and in his second publication he excluded the third group altogether. None of his own cases belonged to the third group; he collected from the literature the cases of capillary angiomas and arteriovenous aneurysms and classified them

129. Laval, J.: Retinitis Exudativa: Coats' Disease, Am. J. Ophth. **27**:163, 1944.

separately, in view of the different clinical picture and pathologic features of capillary angioma. Von Hippel stated the belief that Coats's third group was a process similar to, but different from, the new formation of retinal vessels in angiomatosis, and stressed the necessity of isolating it from exudative retinitis, in which the primary change is the extensive subretinal bleeding, leading through organization to massive tissue formation of the outer surface of the retina. In Leber's opinion, the hemorrhages were incidental and secondary, the primary change being inflammatory and exudative, and he designated the disease as serofibrinous degenerative retinitis. Leber called attention to the presence in Emanuel's case of colloid degeneration and tumor-like colloid masses at the outer surface of the retina, in a distribution similar to that of serofibrinous exudation and infiltration in exudative retinitis.

The retinitis exudativa externa, or retinitis hemorrhagica externa, of Coats is a slowly progressive disease characterized by massive exudation. Elwyn [130] called it a distinct clinical entity; he stated that the exudation and connective tissue formation in the retina are consequences of local circulatory disturbances, beginning with transudation due to peristasis and prestasis, and of rupture of small dilated vessels based on congenital vascular malformation. Duke-Elder, on the other hand, expressed the opinion that Coats's disease is by no means a clinical entity and included a considerable number of conditions, such as senile exudative choroiditis, which often is called the senile form of Coats's disease. That massive retinal exudation may accompany other retinal diseases became well known, as, for instance, in cases of senile macular degeneration in which the clinical and pathologic features of exudative retinitis (Axenfeld, Coppez, Danis, Feingold, Woelfflin) were often encountered. But in age incidence and the usually bilateral appearance of the disease, the senile form is unlike the type described by Coats, and even if occasionally massive external exudation is present, its inclusion under the heading of Coats's disease does not seem justified. Only the circumstance that Coats's disease is often hard to define clinically and pathologically, that cases show similar and dissimilar characteristics and that the changes show wide variation according to the duration of the disease is responsible for the occasional confusion of cases of a different disease entity showing massive exudation with cases in which the massive exudation is the significant feature. In Woelfflin's [131] case there was fibrous proliferation with involvement of the glial elements. The process was of long standing, and degenerative changes dominated

130. Elwyn, H.: The Place of Coats's Disease Among Diseases of the Retina, Arch. Ophth. **23**:507 (March) 1940.

131. Woelfflin, E.: Beitrag zur pathologische Anatomie der Retinitis exsudativa externa, Arch. f. Ophth. **117**:33, 1926.

over the inflammatory ones. There were only small hemorrhages; no cholesterol crystals were present, and the exudation invaded the retina from the choroid.

The senile group of bilateral changes seems to be more closely related to the senile disk-shaped changes of the macula than to the disease described by Coats, granted that occasionally the exudation reaches a degree approaching the massive exudation characteristic of the latter. Emanuel's case demonstrates how difficult it is in a given case to differentiate even the microscopic pictures, not to mention the purely clinical findings. In his case the retinal changes alone indicated Coats's retinitis, but the presence of angioma of the ciliary body contraindicated this diagnosis. The primary pathologic feature was represented by the proliferation of the angioma of the ciliary body into the periphery of the retina, with its always poorer vascularization, so that the secondary picture simulated Coats's retinitis. Emanuel even considered the possibility that some of the cases of retinitis exudativa externa of Coats's first and second groups were possibly cases of undiagnosed angiomatosis of the retina. In one of his later publications, von Hippel included the case of Emanuel in his group; contrary to von Hippel's theory was the opinion expressed by Berg,[132] who stated that the new formation of vessels on the inner surface of the ciliary body was not of tumorous nature, but represented only sprouting vessels of secondary nature. Berg went even further and stated that the eye in Collins' original first case and the second eye of the same patient, described by Wood, presented typical pictures of retinitis exudativa externa. According to Berg, in the second of the two eyes described by Collins, and in the cases of Czermak and of von Hippel, the tumor-like nature of the newly formed vessels is questionable. Similarly, in his opinion, Guzman, Meller and Ginsberg did not definitely prove the tumorous nature of the glial proliferation; even the proliferation into the choroid is not of decisive importance, as the same process is known to occur in various retinal diseases without tumor formation of the glia. Berg did not accept external exudative retinitis and angiomatosis of the retina as different processes, but stated that they were identical, the difference being only in extent and the stage of development. True, Berg's studies antedated Lindau's discovery, but even in that period Leber emphasized that the late stages of angiomatosis of the retina may show more and more the characteristics of Coats's disease, and Rados [133] sharply differentiated von Hippel's disease from that of Coats's.

132. Berg, F.: Beitrag zur pathologische Anatomie der Retinitis exsudativa, Arch. f. Ophth. **98**:211, 1919.

133. Rados, A.: Ueber die Veränderungen im Frühstadium der Retinitis exsudativa, Arch. f. Ophth. **105**:973, 1921.

One of the first observers, Morton,[134] noted, in a case of unilateral angiomatosis, that the enormous masses of exudate were densest at the periphery of the retina and along the course of the main branches of the retinal vessels. The exudate was located beneath the retinal vessels; only a few of the vessels were obscured. The vessels showed narrowing of the lumen, white sheathing, fusiform and globular expansions and rosary-like outline, with occasional association with hemorrhages. Tortuosities, loops, kinks and glomerular formations were encountered. Small pigment patches were present beneath the exudate and in parts of the retina free from the latter. Pathologic examination by Coats showed the presence of leukocytes in the subretinal space, a large mass of fibrous tissue between the retina and the choroid, but more intimately connected with the former, and blood and cholesterol crystals. The vessels in some places stained imperfectly; in others enormous dilatation or thrombosis was noted. In the same early period, Holm[135] gave a clinical description of 10 cases and concluded that retinitis exudativa externa and retinitis circinata belong to the same group. Tresling, whose case doubtless represented typical angiomatosis of the retina with a hereditary tendency, described a nodule in the retina of the younger brother and noted that the exudative changes present recalled those seen in Coats's retinitis; referring to Coats's statement in his first publication, i. e., angiomatosis of the retina may represent external exudative retinitis with arteriovenous communication, he suggested that retinitis circinata, Coats's retinitis and angiomatosis of the retina are modifications of the same process. Gourfein-Welt[136] concluded that exudative external retinitis is not an entity but the final stage of unilateral angiomatosis of the retina, and she compared it to retinitis proliferans. The latter is the appropriate designation of retinal changes following hemorrhages in the vitreous and in the internal layers of the retina; the former, Coats's retinitis, is the counterpart of changes following hemorrhages in the outer layers, and the hemorrhages in angiomatosis of the retina are the mechanism involved in producing changes described by Coats as a separate disease entity. Her conclusions were based on bilateral involvement, without a hereditary trend; the left eye showed a large white patch temporal to the disk, the patch being divided in half by an artery running through the center. The caliber of the artery increased toward the periphery, to become tortuous, and disappeared in the detached retina. Vitreous hemorrhages and irido-

134. Morton, A.: A Peculiar Form of Retinal Disease, Tr. Ophth. Soc. U. Kingdom **28**:214, 1908.

135. Holm, E.: Retinitis exsudativa externa, Klin. Monatsbl. f. Augenh. **59**:319, 1917.

136. Gourfein-Welt: In welcher Beziehung steht die Retinitis exsudativa zur Angiomatosis retinae? Klin. Monatsbl. f. Augenh. **64**:105, 1920.

cyclitis with secondary glaucoma developed in the later course of the disease. In the macular region of the right eye was a small, sharply outlined, deep red spot, connected with a small, tortuous vessel, the lesion representing a minute angioma. Slides of the right eye revealed the presence of an angioma, which had not been detected with the ophthalmoscope. Clausen described uniocular typical angiomatosis of the retina, the bulging exudate in the retina suggesting Coats's disease. Not only was sharp differentiation of the two diseases impossible; but the many mutual characteristics suggested that the two pictures probably presented the same pathologic process. The delicate glial proliferation at the margin of the tumor was accompanied with coils and nodules of vessels, indicating that the primary pathologic process was vascular and the reaction of the glia only secondary. The adjacent portions of the choroid showed changes in the pigment epithelium and dilated choroidal vessels, indicating a simultaneous involvement of the choroid. In Erggelet's case of bilateral involvement the clinical findings were those of angiomatosis of the retina, but anatomically the case represented external exudative retinitis. Miyashita and Nisyake described a questionable case of angiofibromatosis followed by general degeneration of the retina, and closely related to von Hippel's disease, in which hemorrhages occurred in the outer and inner retinal layers, whereas in Coats's retinitis the primary hemorrhage is in the outer layers only and is followed by hyperplasia of the connective tissue elements. Heine accepted the existence of von Hippel's and Coat's diseases as separate entities, but pointed out the possibility of transitional forms (Clausen) or of apparent transitions through similarity of the clinical pictures. The clinical picture may present difficult problems in differentiation. Snell described a case of varix-like, dilated veins with a globular, cystlike detachment of the retina. There was no definite change in size, shape or structure of the retinal arteries and veins, no anastomosis of arteries and veins, no hemorrhage, exudate or cholesterol crystals. The alterations were interpreted as primary vascular changes affecting the outer reticular layer, but Arnold Knapp concluded that the condition was either angiomatosis of the retina or a form of Coats's retinitis.

Berg based his opinion on the histologic study of 4 cases and, as already mentioned, included angiomatosis of the retina with Coats's retinitis (retinitis exudativa). Without affirming this conclusion, one must consider the histologic features. The primary disease, according to Berg, is a vascular change, leading to hemorrhages of various sizes within the retina and in the subretinal space, followed by serous or serofibrinous exudate with necrosis of the retina. Formation of connective tissue between the two membranes, the retina and the choroid, detachment of the retina, and desquamation and proliferation of the pigment epithelium cells were further sequelae. The central vessels were

normal; the vascular changes increased toward the periphery. The latter consisted in proliferation of the endothelium, round cell infiltration, dilatation with destruction of the walls, hyalinization, thrombosis, aneurysmal formation, shrinking of vessels, disappearance of the lumens and formation of hyaline stripes. The early stages proved that the exudation was due to the hemorrhages; necrosis occurred only in the neighborhood of thrombosed and grossly changed vessels, bearing out Coats's concept that the pathogenesis is in the hemorrhages. One cannot agree with the conclusion that in external exudative retinitis the changes are widespread, that in the early stages of von Hippel's disease the identical changes are localized in a small sector, that the vascular changes with retinal and subretinal hemorrhages are similar and stimulate secondary glial proliferation and choroidal changes without extensive detachment of the retina, and that the small nodule is the earliest manifestation of Coats's disease with chorioretinal synechia. According to Berg, von Hippel's disease is only a variation of exudative retinitis, an opinion which can hardly be supported by the facts.

Rados described a very early stage of Coats's disease in a 2 year old child; the ophthalmoscopic picture of the initial changes is seldom obtained; accordingly, it was reproduced in the paragraph on retinal diseases by Schieck.[137] Applemans [138] similarly referred to Rados' publication in comparing initial changes of angiomatosis of the retina with that of retinitis exudativa externa. In the observation of Rados, there were three isolated patches in the retina around the disk; these were white later and changed to bluish yellow. The isolated patches increased in size and became confluent, without detachment or visible retinal bleeding. Pathologic examination revealed that the changes were localized at the posterior pole around the disk, resulting in a button-shaped swelling of the retina. In the affected parts all the retinal layers were folded, the outer more than the inner layers, producing a tubular or ring-shaped formation of the layer of rods and cones. There were glial proliferation and swelling of the ganglion cells with nuclear destruction. Between the internal limiting membrane and the ganglion cell layer small hemorrhages were present, but none could be detected in the middle or outer layers. The vascular pathologic change was intense, proliferation of cells of the intima and adventitia leading to obstruction of the vessels. There was a serofibrinous exudation throughout the retina, especially of the internal layers, with the formation of delicate exudate at the inner surface of the internal limiting membrane. Between the retina and the choroid were an exudate rich in albumin and a con-

137. Schieck, E., and Brückner, A.: Kurzer Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 5, p. 520.

138. Applemans, M.: L'angiomatose de la rétine chez l' enfant, Arch. d'ophth. **7**:489, 1947.

nective tissue layer rich in cells and vessels, with proliferating pigment epithelium elements. The changes were of inflammatory nature with pronounced pathologic changes in the vessels. The vascular changes were the primary ones and were followed by progressive nutritional disturbances of the retina, which, in turn, became regressive in the later stages, overshadowing the preceding inflammatory changes. The study of Rados antedated Lindau's work by many years; in his concept, nevertheless, the exudative retinitis of Coats was strictly separated from angiomatosis of the retina.

Scheerer,[139] in his classification of degenerative retinal disease, created two groups. His first group included the retinitis exudativa of Coats, von Hippel's disease and Leber's disease (hereditary optic atrophy). The common characteristics were given as the occurrence in youth and the predilection for males. The last two diseases are based on a primary disturbance in the vascular system, or a disturbance in the development of the vascular system, possibly on a congenital basis. Angiomatosis of the retina is proved through bilaterality and a familial tendency not only of the retinal angiomatosis with cystic degeneration, but of the association with systemic cystic tumors. Leber's disease, according to Scheerer, is, similarly, a primary disturbance of the circulatory system, though the familial occurrence and systemic involvement do not belong to the picture. In Coats's disease the vascular changes are not predominant; the dilatation and aneurysms were observed in only a few cases, but it is questionable whether these cases belonged in the von Hippel or in the Leber disease group. Under the second group he included retinitis circinata (Fuchs and Goldzieher) and the disciform changes (Junius and Kuhnt); the congenital disposition of the vascular changes could not be considered; rather, the changes are senile. Diseases of the second group affect women of advanced age predominantly.

Ten Doesschate[140] came to the conclusion that retinitis exudativa externa is not an entity, but is only the mode of reaction of the retina to various agents. In 1 of his cases a ring around the disk in the subretinal space caused the retina to bulge forward, the ring consisted of fibrous tissue, poorly vascularized and with flat nuclei, hyaline-like substance and cholesterol crystals; in other parts were masses of large vacuolated cells, reminding one of swollen pigment epithelium elements. In the second case necrosis of the sclera accompanied the massive retinal and subretinal changes. Junius[141] differentiated between Coats's and

139. Scheerer, R.: Netzhaut und Sehnerv, Ergebn. der allg. Path. u. path. Anat. **2**:1 and 152, 1895.

140. ten Doesschate, G.: Ueber Retinitis exsudativa externa, Klin. Monatsbl. f. Augenh. **79**:505, 1929.

141. Junius, P.: Zur Aetiologie der Retinitis exsudativa Coats, Klin. Monatsbl. f. Augenh. **92**:748, 1934.

Leber's disease; the former is a primary retinal hemorrhage extending into the subretinal space with secondary massive exudation; the latter, a necrotising type of inflammation of embolic-toxic nature. In Leber's disease (hereditary optic atrophy) the primary change is the miliary aneurysm, followed by retinal degeneration, while in Coats's disease the vascular changes are only of secondary nature. Zinsser mentioned that mild and severe forms of Coats's disease are encountered; the first may show transition to other degenerative retinal diseases (retinitis circinata, or Junius-Kuhnt disease) belonging to different age groups; the second may harbor angiomatosis of the retina, which differs in bilateral involvement, familial occurrence and pathologic changes in other parts of the body. The glial proliferation is common to Coats's and to von Hippel's disease, and, similarly, the massive exudation behind the retina, which occurs in the late stages of angiomatosis, recalls the clinical picture of Coats's disease. The glial proliferation associated with the massive exudation is frequently the cause of an erroneous identification; the two diseases show only similarities; they differ entirely in origin. The differential diagnosis may cause considerable difficulty, as, in spite of the different genesis, similarity of symptoms may obscure the origin of the changes. According to Zinsser, the change in the capillaries of the skin demonstrating the mesenchymal malformation of the anlage aids in the differentiation of the two entities.

Marchesani [142] did not accept Lindau's sharp differentiation. His observation included 2 patients; the first, a child 2½ years of age, with a clinical diagnosis of glioma; the second, a woman aged 38, with angiomatosis of the retina. The second patient exhibited loops of vessels with glial collars. The glia was rich in fibrils and poor in cells; the slow progression and benign nature suggested the erroneous diagnosis of astrocytoma. According to Meller, the retinal tumor consists of the singular glia cells of the retina, the Müller fibers. The tumor in his second case was in a late stage. Marchesani considered the changes present in his first case, in which the picture confirmed Meller's, as long Müller fibers in neoplastic formation, with proliferation and fibrillar formation in the late stages; the histologic diagnosis, unlike the clinical diagnosis of glioma, was external exudative retinitis with proliferated and dilated vessels. Marchesani referred to the second group described by Coats, in which vascular loops, newly formed vessels, dilated vessels and aneurysms occur. These changes are not necessarily on an infectious-toxic basis but, in the opinion of some observers, may represent primary changes. Marchesani noted that in some cases reported in the literature external exudative retinitis was classified by others as angiomatosis of the retina (Lindau), and, conversely, that angiomatosis

142. Marchesani, O.: Zur Anatomie der Angiomatosis retinae und Retinitis exsudativa, Arch. f. Augenh. **103**:633, 1930.

(as in the often quoted and differently interpreted case of Emanuel) was considered by other authors as Coats's disease. The differentiation does not seem justified; Coats's and von Hippel's disease have the common characteristics of exudation and vascular changes, and the latter in some cases of external exudative retinitis must be considered primary. In his first case the changes in the optic nerve pointed to the primary nature of the pathologic process in the vessels and therefore, of the exudation; the detachment of the retina and the glial proliferation represented changes of secondary nature, indicating that in some instances Coats's disease is based on angiomatous formation of vessels. Marchesani's opinion remained essentially unsupported. Von Hippel emphasized that the late stages of angiomatosis of the retina are difficult to differentiate anatomically, but that it is not permissible not to separate the two entities. The exudative retinitis of Coats develops on a different etiologic basis, and the late stage of angiomatosis, in spite of similarities, is certainly not identical with Coats's disease. The early stage of the clinical picture in angiomatosis and the absence of angioblastic proliferation in Coats's disease justify the sharp separation of the two diseases. The anatomic picture alone cannot furnish the dividing line in all cases; vascular changes are present in both, but tumor formation of the vascular elements occurs only in angiomatosis.

Oguchi described a case of bilateral acute external exudative retinitis (type 1 of Coats) associated with a tumor of the right cerebellopontile angle and proposed to widen the scope of Lindau's disease to include not only angiomatosis of the retina and brain, but the gliomatosis and the intermediate type, Coats's disease. The clinical findings seemed to be equally confused in the case of Avizonis, in which the left eye was blind for two years and showed cataracta complicata accreta, and the right eye had preretinal and vitreal hemorrhages. After the vitreous hemorrhages had cleared, Gonin diagnosed the condition as angiomatosis of the retina. Avizonis described retinal hemorrhages adjacent to the nodule with retinitis proliferans. Hesse [143] described capillary angioma with endothelial and perithelial elements, sequelae of exudative retinitis, as the main constituents. Hesse disagreed with Oguchi that Coats's and von Hippel's disease cannot be differentiated; on the other hand, he disagreed with authors who advocate a sharp separation; external exudative retinitis is not a disease *sui generis*, but a symptom complex arising on different bases, one of which is angiomatous tumor formation.

While the original presentation of Coats was based on 11 cases (4 females, 7 males), Coste's [144] review listed 51 cases (29 males, 22

143. Hesse, R.: Ueber die anatomischen Grundlagen der von Hippelschen Netzhauterkrankung, Ztschr. f. Augenh. **79**:252, 1933.

144. Coste, M.: Contribution de l'étude de la rétinite de Coats, Thesis, Paris, Vigot Frères, 1938.

females), to which Lamb[145] added 8 of his own. Lamb stated that the essential change was infiltration of the retina in whole or in part with albuminous or edematous fluid, leading to accumulation of exudate under the retina and resulting in complete or partial detachment of the latter. The late stages (2 cases) were distinguished by the presence of a large amount of connective tissue within or between the retina and the choroid. He stated that the exudative process was diffuse throughout the retina and did not occur in the external layers only; on the contrary, the larger part of the fluid entered first the internal plexiform ganglion cell and nerve fiber layers. The pigment epithelium cells were transformed into macrophages and then into fibroblasts, and their further proliferation was responsible for the dense masses of connective tissue. The masses were usually at the posterior pole, but not uncommonly were located at the periphery. Vessels were tortuous or looped, with occasional anastomosis. Hemorrhages were frequent, and often cholesterol-like glistening deposits were noted. In MacDonald and Lippincott's observation the right eye was examined only anatomically; in the left eye the diagnosis might have been either angiomatosis or Coats's disease, but the changes in the vascular system of the retina favored the first possibility. The case demonstrated, again, the possibility that extensive gliosis may mask the true nature of the vascular derivation of the tumor. Rumbauer, similarly, differentiated between retinitis circinata and retinitis exudativa, and between the latter and angiomatosis of the retina, but accepted possible similarities in the late stages of angiomatosis. Appelmans mentioned the presence of endothelial proliferation, hyaline degeneration and thrombosis of vessels of the second and third grades, especially the precapillary veins, in both diseases, but stated that the absence of tumor formation, a hereditary factor and systemic changes in retinitis exudativa, together with its unilateral occurrence, warrant the sharp differentiation.

Junius attempted to correlate Coats's and Leber's retinal degeneration with multiple miliary aneurysms with Osler's hereditary familial telangiectasis. The primary disturbance in Osler's disease is a defect of the mesenchymal tissues, which fail to form a normal endothelial lining of the vessels and normal supporting tissue. Junius conjectured as to the possibility that the miliary aneurysms of the retina might be the equivalent of telangiectasis of the skin and mucous membranes and that they might represent a localized defect in mesenchymal differentiation. In refutation of Junius, however, it should be stressed that Osler's disease is a systemic condition with proved hereditary transmission; furthermore, that in proved cases of Osler's disease miliary

145. Lamb, H. E.: Exudative Retinitis, Am. J. Ophth. **21**:618, 1938.

aneurysms of the retina have not been observed, and that, on the other hand, in cases of Leber's disease the systemic involvement characteristic of Osler's disease is not present.

Elwyn expressed the belief that the inflammatory explanation of retinal hemangioblastoma (Leber, Lamb) was not acceptable, as the essential elements of inflammation, such as infiltration of leukocytes and involvement of the choroid, are not present despite the necrosis in the retina. The changes are to be explained by local circulatory disturbances only. Dilatation of smaller vessels was mentioned by the majority of investigators, being noted in 7 of 9 cases by Coats; narrowing and dilatation of vessels, thrombi and dissecting aneurysms were mentioned in 4 cases by Berg, and dilatation in the early stage was noted by Rados, Zinsser, Marchesani, ten Doesschate, von Hippel and Lamb (4 of 8 cases). According to Elwyn, despite cases in which vascular changes were not reported, they constitute the primary change, and Coats's disease is based on congenital malformation of certain areas of the retina. This malformation should affect the small vessels, arteries, capillaries and veins, with dilatation of vessels and defective walls, subject to hyalinization, thickening or thinning, and ensuing rupture and aneurysm. In the classification of vascular malformation and vascular tumors of the brain by Bergstrand, Olivecrona and Tönnis,[146] external exudative retinitis was included with telangiectasia. Coats himself considered the primary change the hemorrhages, due either to an abnormal constitution of the blood or to primary changes in the smaller vessels. Elwyn's contention eliminated the first and based the pathology of Coats's disease on a congenital malformation, without furnishing definite proof for his consideration. Davenport [147] remarked that, despite the fact that evidence was advanced (Heijl) to prove the congenital origin of Coats's disease, proof does not yet exist.

Davenport called attention to the fact that in many vague cases showing retinal exudate and organized plaques of fibrous tissue the disorder may have been loosely called Coats's disease. In late stages angiomatosis and Coats's disease may be similar, but the early picture is dissimilar, and the unity of the two entities is therefore hardly acceptable. Applemans mentioned the similarity of the vascular lesions but stressed that the early stages of Coats's disease are inflammatory, almost always unilateral and without hereditary, familial or systemic involvement.

146. Bergstrand, H.; Olivecrona, H., and Tönnis, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns, Leipzig, Georg Thieme, 1936.

147. Davenport, R. C., Inflammatory or Vascular Atypical Coats' Disease, Tr. Ophth. Soc. U. Kingdom **58**:178, 1943.

Endothelial proliferations, hyaline degeneration and thrombosis of the vessels of the second and third grades, especially the precapillary veins, are constituents of external exudative retinitis, but the angiomatous formation occurs exclusively in angiomatosis and does not permit the unification of the two distinct entities.

DIFFERENTIAL DIAGNOSIS OF ANGIOMA AND HEMANGIOBLASTOMA OF THE RETINA

According to Virchow, hemangioma is a tumor formation of blood vessels. Cavernous angioma is less frequent and is composed of large blood spaces separated by their walls. Racemous angioma is characterized by the separation of the vessels by interposed tissue. The angiomas are tumors consisting of newly formed vessels, or of vessels with newly formed elements of the vascular walls, or of both. Their differentiation from telangiectasia or nevus vaculosus is difficult, as the endothelial budding and the formation of netlike, syncytial elements with secondary canalization is often extremely hard to prove. Virchow considered the angiomas true blastomas and differentiated arterial venous and capillary types, according to their respective origins, the capillary type being apparently the most frequent. The angioma racemosum arteriale may originate from one or from many adjoining arteries, the branches showing tortuosity and dilatation; the vascular neoplastic process may reach the veins through the capillaries. The tumor is characterized by dilatation and complex intertwining of many newly formed and altered vessels of small caliber, with subsequent involvement of the normal vessels. The vessels have few or no lateral anastomoses; the tumor formation affects only an isolated segment of the vessel walls, producing elongation and varicosities in a closed area, without gradual involvement of the adjacent vessels. The capillary angioma consists of a network of newly formed capillaries. The new formation effects one segment of the vessel only, from which buds of endothelium grow out and form new capillaries, resulting in a more or less closed system of vessels. The endothelial cells are large and swollen and may be several layers in depth. The endothelial proliferation may be pronounced and lead to occlusion of the lumens, so that the picture is one of a solid mass of cells with little or no evidence of vascular lumen, a condition often designated as hemangioendothelioma, or endothelioma.

Virchow's subdivision of the angiomas became untenable after the discovery of the arteriovenous aneurysm of the brain by Steinheil in 1895, and the recognition of Sturge-Weber disease (nevoid amentia), consisting of the triad of congenital glaucoma, ipsilateral nevus flammeus of the face, chiefly in the distribution of the trigeminal branches, and contralateral epileptiform seizures. The basis of the seizures is an intra-

cranial vascular anomaly, an isolated type of angioma racemosum, differing from the usual angioma racemosum venosum. Bergstrand classified the vascular tumors of the brain as follows:

A. Angioma cavernosum

B. Angioma racemosum

1. Telangiectasis
2. Sturge-weber disease
3. Angioma racemosum arteriale
4. Angioma racemosum venosum
5. Aneurysma arteriovenosum

C. Angioblastoma (Cushing and Bailey), or angioreticuloma (Roussy and Oberling), or Lindau's disease

D. Angioglioma

Owing to the circumstance that Sturge-Weber disease shows disturbances of the central nervous system and port-wine nevi of the skin, the disease was classified with the tuberous sclerosis of Bourneville, the neurofibromatosis of von Recklinghausen and the familial hemangiomatosis of Lindau as belonging to the congenital neurocutaneous dystrophias (Tonnis), or to congenital neuroectodermal dysplasias (*syndrome neurocutané or dysplasies neuro-ectodermique congénitales*, von Bogaert). The dysontogenetic changes are associated with neoplastic proliferations of glia, nerve fibers or vascular elements. The changes do not occur exclusively in the ectodermal layer; the dysontogenetic hereditary blastomatous development is of ectomesodermal origin. There are numerous common characteristics of the group; the adenoma sebaceum (Pringle) occurs not only with tuberous sclerosis but, in rare instances, with neurofibromatosis; the close relation of the two entities is demonstrated by the alteration of the two within the same family (Oehler). In Sturge-Weber disease, tumors (glioma [van der Hoeve, Scheinker], hypernephroma [Ostertag], acromegaly [Ginsberg] and pigment spots of the skin [de Morsier and Franceschetti]) were observed, pointing to a close interrelationship in the group. This interrelationship was illustrated in the unique observation of Delay and Pichot,[148] in which a girl had Sturge-Weber disease, and the father and 2 brothers, intracranial lesions, one of the brothers also presenting retinal angiomatosis. The authors suspected identity of the genes and proposed to combine Sturge-Weber and von Hippel-Lindau disease under the head of familial angiomatous phakomatoses. Van der Hoeve created the classification of phakomatosis, including the four entities. Phacoma differs from the nevi of the skin in the absence of histologically characteristic nevus cells; it represents an elevated, con-

148. Delay, J., and Pichot, P.: La phacomatose angiomateuse familiale, Rev. neurol. **78**:151, 1946.

genital, hereditary spot, either not changing, or changing only slightly, its size or undergoing blastomatous changes to become a phakoma, and, according to the structural elements, forming adenophakoma, fibrophakoma, angiophakoma or a genuine tumor, phakoblastoma.

Angiomatosis of the retina (von Hippel–Lindau disease) seems to fall clearly within the group of hereditary blastomatosis, which represents a disturbance affecting the earliest stages of development. In first part of this paper, in the clinical description, an accurate picture of the funduscopic appearance was given, and it was emphasized that the tumors are chiefly of peripheral location with dilated afferent and efferent vessels, the tumor itself being smooth surfaced, without dilated vessels within the mass. Infrequently the tumor appears at the posterior pole or at the disk. In the cases of Carr and Stallard; Niccol and Moore; Brain; Brain, Greenfield and Northfield, and Gourfein-Welt the angiomatous tumor was close to the disk; in Lotman's case a small tumor lay at the upper and a large mass at the lower margin, almost covering the disk, and Putchar's reexamination of the tumor in Schieck's case demonstrated the presence of angiomatosis at the disk itself.

In the clinical description of their case, Niccol and Moore's noted that the tumor was of raspberry appearance, immediately adjoining and partly covering the temporal edge of the disk. The patient was 32 years of age; in the opinion of the authors, the tumor may have been present since birth, but had increased recently in size. The tumor was sharply defined and projected about + 3.0 D. into the vitreous. The mass consisted of cavernous spaces lined with endothelial cells and containing blood. Feig's[149] observation seems to belong in the same category. In the region of the disk a network of blood vessels, consisting of an upper and a lower layer and entangled with each other, covered an area approximately six or seven times that of the disk; the disk itself was invisible. In the periphery of the choroid, white, degenerative areas were noted with and without pigmentation and vitreous hemorrhages, but retinal changes were absent; only partial detachment was present. The eye was hypotonic; cerebral symptoms were not noted, and, in Feig's opinion, the tumor was an angioma, but not angiomatosis. In the case of Cross[150] there was gray swelling at the nasal margin of the disk with several dilated veins, which increased rapidly in size. Above and to the nasal side of the swelling retinal hemorrhages were visible. Because of the possible malignant nature of the tumor, enucleation was decided on, and the pathologic examination disclosed vascular formation at the margin of the disk and

149. Feig, I.: A Case of Angiomatosis Retinae, Brit. J. Ophth. **22**:295, 1938.
150. Cross, A. C.: Angioma of Retina, Brit. J. Ophth. **27**:372, 1943.

retina, invading the optic nerve but not the choroid. There were endothelial channels, varying from capillaries to vessels as large as the main branches of the central artery and vein, and the supporting framework contained glial elements.

The condition in 3 cases last mentioned showed some relation to but differed distinctly from retinal angiomatosis. The location of the tumor at the disk, its raspberry-like surface, the participation of large vessels, the absence of exudative or degenerative changes in the adjacent parts of the retina, the unilateral occurrence (never symmetric) and the absence of hereditary and systemic involvement form the basis for differentiation from the hemangioblastoma. Feig's conclusion that the lesion represents an angioma of nondestructive character is logical. This tumor must be considered a congenital malformation of blood vessels, which enlarges by expansion of the preexistent vessels, without proliferation of the cells or endothelial budding, in contrast to the hemagioblastoma, which is characterized by proliferation of embryonic vessels.

Angiomas of the racemose group were considered genuine tumors in the older literature. The possibility of tumorous growth in varying degrees was an attributed characteristic of vessels of all three types—the arteries, the veins and the capillaries—and the proliferating tendency was thought to involve the adjacent parts both centrifugally and centripetally. Later it was proved that the thickening of the walls of the vessels in angiomas is not tumorous, but depends on the mechanical effect of the circulation. The criterion of tumor-like growth is the endothelial budding. The contention that a developmental disturbance was the causative factor in angiomas became increasingly popular with time. Opinions, explaining the vascular proliferation as an autonomous growth, on the one hand, or as a tumor of dysontogenetic origin, on the other, are still divided. The dividing line between genuine blastomas, hyperplastic proliferations and tumor-like developmental malformation is not sharp. But the angiomas, either tumors in the strict sense or vascular malformations, represent a separate group among the diseases of the retina, and the terms angioma and angiomatosis of the retina (hemangioblastoma of von Hippel and Lindau) should not be used interchangeably.

31 Lincoln Park.

SLIT LAMP MICROSCOPY OF THE POSTERIOR SECTION OF THE EYE WITH THE NEW PRESET LENS

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THE RECENT introduction of my preset lens into the United States by lectures of Lindner,[1] as well as the fact that this lens is now being manufactured in the United States under the name the "Hruby diagnostic lens" gives me an opportunity of publishing a short paper on my technic of examination.

Only thirty years have passed since the slit lamp was used for the first time for examination of the posterior section of the eyeball through the efforts of Koeppe.[2] He was the first to recognize that the deeper parts of the eye can be made visible only if, in general, two conditions are complied with. These are, on the one hand, the smallest possible angle between the optical axis of observation and that of illumination, and, on the other, such an intense dispersion of the rays coming from the depth of the eye and leaving it that they seem to be coming from a fundus image virtually situated within the focus of the objectives of the observation microscope. As is well known, the first condition was accomplished by Koeppe [2] by using a silver mirror which reflects the pencil of rays into the eye at an acute angle; the second condition was complied with by a contact lens. The fact that Koeppe's method has made only a little headway in practice was due to technical difficulties. Therefore various attempts were made to improve and simplify the method; a brief survey of them follows.

Gallemaerts and Kleefeld [3] (1922) modified Koeppe's silver mirror by fitting the slit lamp vertically. In this way the use of the usual observation microscope, instead of the special microscope with the mono-objective (Bitumi) used by Koeppe on account of lack of space, was made possible. L. López,[4] (1925) proceeded in a similar way; besides, he connected the microscope and the illumination hand in such a way that the focal adjustment remained unaffected by any movements of the microscope.

From the Second Eye Clinic of University of Vienna.

1. Lindner, K.: Ophth. Gesellsch. Heidelberg, 1936, p. 435.
2. Koeppe, L.: Arch. f. Ophth. **95**:282, 1918; Die Mikroskopie des lebenden Auges, Berlin, Julius Springer, 1922.
3. Gallemaerts, E., and Kleefeld, G.: Ann. d'ocul. **159**:264, 1922.
4. López, L.: Rev. gen. d'opht. **39**:383, 1925.

Enriquez López [5] constructed a double mirror which seemed to promise certain technical advantages by increasing the possible number of angle combinations; but the mirror was not easy to handle, and through the double reflection, the slit beam was twisted by 90 degrees from the original direction.

While these modifications of the silver mirror did not succeed in obtaining any considerable results in simplifying Koeppe's technic, the introduction of Lindner's (1936) "angled microscope" brought about a definite advance.

Lindner obtained the necessary reduction of the angle which exists between the optical axis of illumination and the axis of observation by deflecting, not the illumination beam, but the observation rays in the microscope. Thus, the procedure of examination became simpler, but the microscope was arranged only for monocular observation. It has, however, been possible to obtain a series of valuable tests by Lindner's method of examination, particularly in regard to the posterior detachment of the vitreous body.

Čavka [6] (1937) also tried to overcome the difficulties of the silver mirror method by setting the slit lamp in the direction of the optical axis, by removing the inconvenient screw of the mono-objective from the right or the left side, as required, and by fitting both oculars of the Bitumi vertically, the upper ocular being used mainly for examinations.

The reduction prism attached to Goldmann's [7] slit lamp model (Haag-Streit, Berne) is, however, the simplest appliance so far produced for reducing the angle in question. If required, it is set in front of the illumination lens of the slit lamp hand and deflects the illumination beam by double reflection in such a way that the angle of the illumination beam and the neighboring tube of the microscope is reduced by from about 13 degrees to 5 degrees. The reduction prism is also manufactured for the slit lamp of Th. Hamblin, Ltd., London.

The necessity of having to use a contact lens for the examination of the posterior section of the eye with the slit lamp has also been felt to offer great difficulty. Any person familiar with the contact lens method knows what technical difficulties are connected with it and what inconvenience for the patient. The contact lens, moreover, permits an examination only in a circumscribed area around the axis, but not of the periphery of the vitreous and the fundus. Therefore many attempts to avoid the contact lens have been made.

Evans' [8] method (1932) is based on the principle of ophthalmoscopy by the indirect method. The slit lamp was placed frontally, and a

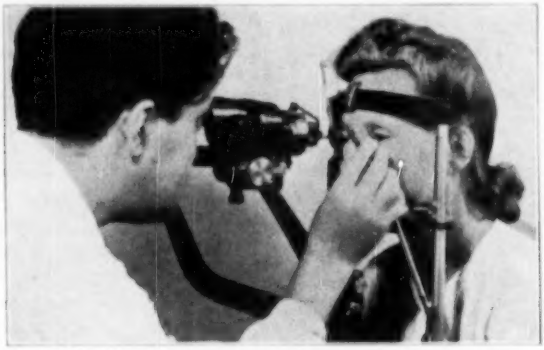
5. López, E.: Klin. Monatsbl. f. Augenh. **95**:77, 1935; ibid. **96**:181, 1936.

6. Čavka, V.: Arch. f. Ophth. **137**:472, 1937.

7. Goldmann, H.: Klin. Monatsbl. f. Augenh. **91**:494, 1933; ibid. **93**:522, 1934; Ophthalmologica **96**:90, 1938.

8. Evans, J. N.: Reflecting Prism-Lens for Slit-Lamp Microscopy of Retina, Arch. Ophth. **8**:274 (Aug.) 1932; Am. J. Ophth. **15**:1144, 1932.

planoconvex lens with a prism attached centrically was fitted at its end. The light beam of the slit lamp was projected into the patient's eye by total reflection through the prism; the rays returning from the eye were joined to an inverted image by the planoconvex lens, and finally the image was observed monocularly through an observation microscope; in this method very great magnifications may be used. I do not know to what extent this method has been adopted and what results have been obtained. The same applies to the method of Enríquez López (1936).[8] By a convex lens which reproduces the slit in the posterior focus plane of the slit lamp lens, the pencil of rays was made, corresponding to the refraction of the examined eye, either parallel, divergent or convergent and was finally reflected into the eye by the double mirror devised by the same author. By means of a Recoss disk, another convex lens was inserted between the upper mirror and the patient's eye. This



Slit lamp microscopy of the posterior section of the eye by means of Hruby's preset lens and fixation device performed with Goldmann's slit lamp of Haag-Streit (Berne).

lens produced an inverted image of the fundus, which was used as an object for the observation microscope.

Zamenhof[9] (1930) dispensed with the slit lamp and, by means of an additional appliance, the "focalizator," the focal illumination of the fundus was made possible with Gullstrand's simplified ophthalmoscope. H. Wolff[10] (1901) and Friedenwald (1927)[11] had already striven for slit lamp ophthalmoscopy.

9. Zamenhof, A.: Arch. f. Ophth. **124**:87, 1930; ibid. **129**:149, 1932.

10. Wolff, H.: Ztschr. f. Augenh. **5**:109, 1901; ibid. **28**:307, 1912.

11. Friedenwald, J. S.: Bull. Johns Hopkins Hosp. **40**:201, 1927; Clinical Studies in Slitlamp Ophthalmoscopy, Arch. Ophth. **1**:575 (May) 1929; Folia ophth. orient. **2**:171, 1936; Disease Processes Versus Disease Pictures in Interpretation of Retinal Vascular Lesions, ibid. **37**:403 (April) 1947.

I myself have tried to overcome the difficulties of the contact lens method by using a preset lens, for neither the modification of the contact lens by Linder nor that by Goldmann was able to lessen the difficulties of the procedure in any appreciable way.

Stilling [12] (1878) had already conceived the idea of neutralizing the refraction of the eye by setting a minus lens with a short focus in front. In this way he thought to make possible the orthoscopic observation of the fundus, and even to observe the fundus image by means of a small scale telescope.

Koeppe, too, discussed the possibility of a preset lens, but he rejected this idea with the following argument:

> Besides, and that would have been the main thing, the anterior plane surface of the glass would have had to be so far away from the eye as not to be soiled by the movements of the eyelashes, but then the objective would have had to be brought much too close to the plane surface, or it might even have touched it. The same applies to the presetting of a minus lens with an intense effect in front of the eye examined, according to Stilling.

Later Lemoine and Valois [13] (1928) worked out a method which they called *Ophthalmoscopie microscopique sans verre de contact*. The fundus was diffusely illuminated by means of a stenopaic lamp and a perforated concave mirror; a minus lens, the strength of which depends on the refraction of the examined eye and the required magnification, made it possible to observe the deeper sections of the eye with the corneal microscope. There the fundus appeared in three zones of illumination, differing as to the grade of brightness. But Lemoine and Valois did not use a minus lens for the examination with the focal beam of the slit lamp, and thus it was possible for Goldmann to state that the use of a contact lens for the observation of the fundus with the slit lamp was "unavoidable."

The use of a preset lens of such great dispersing effect for the slit lamp microscopy of the posterior section of the eyeball was first published by me in 1941.[14] My method was then further developed on Goldmann's slit lamp (Haag-Streit, Berne), and for the moment this instrument seems to be best qualified for practice of my method. The close mechanical and optical coordination of the slit lamp and the observation microscope, combined with the aforementioned reduction prism, insures a very simple handling of the instrument for the posterior section of the eye, so that the observer can completely concentrate on the eye examined.

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12. Stilling, I.: Verhandl. d. Naturf. u. Ärzte, 1878, p. 116; Klin. Monatsbl. f. Augenh. **17**:52, 1879.

13. Lemoine and Valois: Clin. opht. **12**:423, 1923.

14. Hruby, K.: Arch. f. Ophth. **143**:224, 1941; ibid. **144**:435, 1942; Klin. Monatsbl. f. Augenh. **108**:195, 1942; ibid. **110**:258, 1942; Arch. f. Ophth. **147**:364, 1944; Wien. klin. Wchnschr. **58**:461, 1946; Ophthalmologica **115**:290, 1948

The advantage of the preset lens as compared with the contact lens was obvious, that is, simple handling, without any inconvenience to the patient; this makes it possible to examine sensitive patients and children, as well as injured eyes and eyes recently operated on, and to carry out uninterrupted serial examinations in certain diseases. The examinations may be of any length or frequency, and the periphery of the fundus is also approachable.

The preset lens is a spherical minus lens of 55 D. and has a slightly convex anterior surface (+ 5.0 D.). Formerly I used to put the lens in a trial frame or hold it with one hand, but lately a special holder has been constructed, which permits the preset lens to be placed in front of the patient's eye in all desired positions. Finally, I have introduced a small fixation device which is attached to the lateral part of the head prop, usually on the side of the eye which is not being examined. The head of the instrument contains a small red bulb, and a revolving cap makes it possible to show the patient red dots of different sizes. With this fixation device, the examined eye can be accurately focused and guided to the right place, a fact which is of great value in observation of certain parts of the fundus. By the introduction of the holder and the small fixation device the preset lens method has now reached such a degree of simplification as to make possible its extensive use in clinics and in practice.

The preset lens produces a somewhat smaller field of vision than a contact lens and shows the fundus in its natural size with variations caused by the refraction of the eye. The examinations with the slit lamp can be performed with less powerful (tenfold) or more powerful (twenty-fold) magnification; more powerful magnifications have in general proved not to be light enough and to be of no practical value.

For the observation of the posterior section of the eye the following technical points must be observed: the best possible mydriasis, good dark adaptation of the examiner, good illumination of the slit lamp and bringing together of the arms of the slit lamp and the microscope until the smallest possible angle is reached; the reduction prism must also be placed in front. The minus lens must be set as near as possible, and it must be well centered. If there are any disturbing surface reflections, the coupled slit lamp system must be turned a little around the common axis.

When the axial part and the adjoining peripheral part of the fundus are being examined, the preset lens remains unchanged in its position; for the observation of the upper and the lower periphery, the lens is slightly moved up and down, respectively, so that the observation is always made through the center of the lens. But for the examination of the extreme periphery a certain decentration of the minus lens is of advantage, for with use of the prismatic deflection of the lens even the

extreme peripheral parts can be observed. When one is examining the lower periphery, the upper lid of the patient must be lifted while the patient is looking down.

When the lateral periphery of the fundus is being examined, the patient looks in the corresponding direction; the coupled slit lamp system is turned a little to the opposite side, and the minus lens is set in front of the examined eye, its center always being coordinated with the new optical axis of observation.

There is no doubt that the binocular observation is superior to the monocular one and should therefore be attempted in every case. All other conditions being the same, the part of the fundus which can be seen binocularly increases, the wider the pupil, the less myopic, or the more hypermetropic, the examined eye is and the closer the present lens can be set in front. In this respect, the preset lens is equal to the contact lens for emmetropic eyes, inferior for myopic eyes and superior for hypermetropic eyes (Bonaventura [15]).

Slit lamp microscopy of the posterior section has yielded as successful results as examination of the anterior section. Even binocular ophthalmoscopy permits observations in diffuse illumination only, and therefore examination with the slit lamp is in many respects more successful. The relation between the two methods is similar to that between observations of the anterior section of the eye in diffuse illumination and observations by means of the slit lamp. Thus, the slit lamp can actually reveal certain conditions of the eye which cannot be found by other methods or, if at all, only imperfectly.

My associates and I use slit lamp microscopy of the posterior section of the eye not so much for examination of histologic details, in the manner of Koeppe, as for discovering larger formal anomalies and topographic relations as they appear with particular distinctness in the optical section; and our examinations are performed mainly with a view to practical utility.

The topographic relations, for instance, in various changes of the vitreous body can thus be ascertained by means of the slit lamp with great accuracy. Especially in cases of posterior detachment of the vitreous we have arrived at many remarkable results by means of examination with the slit lamp which so far have not been obtainable by other methods. In cases of retinal detachment we could not longer do without the slit lamp, particularly for examining and finding out suspected retinal defects, for discovering very flat detachments and for diagnosing choroidal tumors, cysts of the retina and retinoschisis. By means of the slit lamp it is also possible in most cases to determine

15. Bonaventura, C. M.: Ophthalmologica **115**:179, 1948.

whether the retinal defects have been caused by vitreous shock, according to the theory of Leber, Gonin and Lindner, or by primary degeneration and atrophy of the retina (Vogt).

In diagnosing papilledema and other changes of the optic nerve, examination with slit lamp is just as valuable as for the analysis of various diseases of the macula; congenital coloboma, cysts, cystoid degeneration, retinal defects and edema and chorioretinitis centralis serosa are to be given first place.

The numerous results which have been obtained by the new method have led me to write a monograph on the subject. It will be published shortly in Vienna, with original illustrations.

The firm of Haag-Streit, in Berne, is at present working out the technical details for making the supplementary instruments for the slit lamp microscopy of the posterior section of the eye, as described in this article.

SUMMARY

The development of slit lamp microscopy of the posterior section of the eye is briefly surveyed. A detailed description of my own new preset lens and its use with the slit lamp of Haag-Streit (Berne) follows. Special attention is drawn to the importance of slit lamp examination of the posterior section of the eye by a brief enumeration of its most important applications. A monograph on the results obtained is to be published shortly.

CORNEAL TRANSPLANTATION

II. Indications and Contraindications

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IN AN earlier report [1] on the visual and cosmetic results of corneal transplantation, the unfortunate effect of the glaring publicity attending this operation was discussed. It was suggested that this tidal wave of optimism has blinded both the layman and the physician to the true facts about corneal transplantation. The general public has been so misinformed about this operation that people have been led to believe that entire "new" eyes can be transplanted to replace diseased ones, and that corneal transplantation is a cure for total blindness. Physicians have been so influenced by this publicity that many have believed the statements that corneal transplantation is attended by visual results as good as, or even better than, cataract extraction.

In the preceding paper,[1] a brief review of the literature on the results of corneal transplantation revealed that there is no accord among ophthalmologists concerning the outcome of this procedure and that there is no commonly acknowledged standard of success. Transparency of the graft has been accepted by most surgeons as evidence of a successful operation. I argued that this is fallacious reasoning and that improvement in vision is the logical index of success in a corneal transplantation. Since 20/200 visual acuity is commonly accepted as the threshold for industrial blindness, it was suggested that a successful corneal transplantation should result in improvement in visual acuity to better than 20/200. In this series of 165 corneal transplantations, visual acuity was improved to better than 20/200 after 22 operations (13 per cent). There was no significant change in visual acuity after 86 operations (52 per cent) and a loss of visual acuity after 57 operations (35 per cent). Twenty of the last operations (12 per cent) resulted in loss of light perception. A significant finding in that study was the striking difference between the number of successful visual results and the number of clear grafts; clear grafts occurred twice as often as improvement in visual acuity. In the entire series of 165 operations, the best visual results were obtained in cases of keratoconus (10 successful results in 35 operations). The poorest results were seen in cases of chemical

1. Stansbury, F. C.: Corneal Transplantation: I. Visual and Cosmetic Results, Arch. Ophth. **42**:813-844 (Dec.) 1949.

burn of the cornea (no successful results). The visual results in secondary corneal transplantations (operations on eyes that have already had one or more corneal grafts) were also poor (2 successful results in 35 operations).

One may appear to be working backward, in a review of a series of operations, in discussing the results of the operation first and the indications and contraindications later. However, when the subject is one concerning which so few pertinent facts are established, as is the case in corneal transplantation, the only objective method of evaluation of the indications for operation is by comparison with the results of the procedure. For that reason, the results in this series of corneal transplantations were analyzed before the present discussion of indications for the operation. The purpose of the present paper, then, is an evaluation of the preoperative findings in this same series of corneal transplantations in view of the postoperative visual results.

REVIEW OF LITERATURE [2]

In 1930 Elschnig,[3] discussing his experience with corneal transplantation, stated that the most favorable eyes for operation were those with dense corneal scars following interstitial keratitis; in his series, 73 per cent of eyes with this type of pathologic change attained successful results. Unfavorable for corneal transplantations, stated Elschnig, were (1) eyes of patients under 14 years of age, (2) eyes with increased intraocular tension, (3) eyes with aphakia and (4) eyes with wide anterior synechias. Elschnig also expressed the opinion that corneal transplantation should not be attempted sooner than one year after any disease process of the cornea had completely subsided.

In 1935 a general review [4] of Filatov's work on corneal transplantation was published in the English literature. Filatov expressed the opinion that the presence or absence of normal corneal elements was the determining factor in the prognosis of this operation. On this basis, he divided eyes suitable for corneal grafts into three categories:

1. Conditions favorable (leukoma with some normal surrounding cornea). This category included (1) leukoma following corneal ulcer; (2) central cicatricial leukoma; (3) superficial leukomas after burns, trachoma or herpetic keratitis, and (4) the deep opacity following parenchymatous keratitis.

2. As in the discussion of the literature on the results of corneal transplantation,[1] references in this paper have been limited to those few men who have performed significant numbers of corneal transplantations.

3. Elschnig, A.: Keratoplasty (translated by E. A. Vorisek), Arch. Ophth. **4**:165-173 (Aug.) 1930.

4. Filatov, V. P.: Transplantation of the Cornea, Arch. Ophth. **13**:321-347 (March) 1935.

II. Conditions unfavorable (lesions without any normal corneal elements). This category included (1) corneal staphyloma, (2) corneal fistula and (3) total cicatricial leukoma.

III. Contraindications (no possibility of improving vision). Glaucoma (particularly buphthalmos) and eyes with faulty light projection fell into this category.

In 1937 Thomas [5] published his classification of eyes suitable for corneal transplantation. He divided eyes destined to have this operation into three groups:

I. Suitable eyes in favorable patients. This group included eyes with an opaque cornea, a fairly normal anterior chamber, reasonably good tolerance to light, normal intraocular tension and a conjunctival sac that was clean and free of gross abnormality.

II. Suitable eyes in unfavorable patients. This category included eyes of babies and patients with considerable nystagmus or photophobia.

III. Unsuitable eyes. In this category Thomas placed eyes with (1) extraocular conditions, such as symblepharon; (2) intraocular conditions, such as anterior staphyloma, adherent leukoma and chronic iridocyclitis with secondary cataract, and (3) combinations of these intraocular and extraocular conditions.

Most ophthalmologists in the United States have followed the tenets laid down by Castroviejo. In 1939 he [6] divided eyes suitable for corneal transplantation into two groups: favorable and unfavorable. Favorable eyes, according to Castroviejo, are those in which (1) the intraocular tension is normal, (2) the diseased ocular tissue is confined to the cornea, (3) the leukoma is not very dense and (4) there are areas of clear, or only slightly scarred, cornea surrounding the graft. Castroviejo expressed the opinion that eyes with central leukoma, interstitial keratitis or advanced keratoconus appear particularly favorable for keratoplasty. He stated that eyes unfavorable for corneal transplantation are those with (1) dense leukoma of the whole cornea, (2) aphakia, (3) increased intraocular tension, (4) corneal cloudiness with densely vascularized pannus and (5) anterior or posterior synechias. Later, Castroviejo [7] elaborated his prognostic classification, dividing prospec-

5. Thomas, J. W. T.: The Results of Corneal Transplantation, Brit. M. J. **1**:114-116, 1937.

6. Castroviejo, R.: Present Status of Keratoplasty, Arch. Ophth. **22**:114-126 (July) 1939.

7. Castroviejo, R.: Indications and Contra-Indications for Keratoplasty and Keratectomies, Tr. Am. Ophth. Soc. **43**:324-330, 1945; Am. J. Ophth. **29**:1081-1089, 1946.

tive eyes into four groups: eyes with very favorable, less favorable, and unfavorable conditions and eyes for which transplantation is contraindicated. He subdivided these groups according to the presenting lesion, as follows:

I. Very favorable
   1. Central corneal opacities
   2. Keratoconus
   3. Interstitial keratitis

II. Less favorable
   1. Corneal dystrophies (excepting Fuchs's type)
   2. Entire superficial opacities without vascularization
   3. Adherent leukoma, if iris can be freed first
   4. Descemetocele, when central
   5. Interstitial keratitis (more benign than in I).

III. Unfavorable
   1. Total corneal scars
   2. Leukomas in corneas in which more than one-half the graft will be surrounded by dense scar tissue
   3. Band-shaped opacity of the cornea
   4. Primary fatty degeneration of the cornea
   5. Deep corneal burns due to tear gas
   6. Extensive corneal opacities due to explosions
   7. Aphakia, particularly after intracapsular extraction
   8. Extensive corneal opacities with pannus-like vascularization caused by burns (chemical or flame)

IV. Transplantation contraindicated
   1. Fuchs's epithelial dystrophy
   2. Corneal opacities with calcareous degeneration
   3. Corneal opacity of pemphigus
   4. Corneal opacity with extensive anterior synechia
   5. Poor cooperation of patient

Franceschetti and Streiff[8] in 1943 described four different types of corneal transplantation. In addition to the usual optical keratoplasty, they advocated tectonic, prophylactic and therapeutic transplantation. They outlined their schema for keratoplasty as follows:

I. Optical keratoplasty. The presence of an anterior chamber is necessary for a favorable prognosis, according to these authors. They listed as favorable for operation (1) the leukoma after serpiginous ulcer, (2) old parenchymatous keratitis, (3) familial corneal degeneration,

8. Franceschetti, A., and Streiff, E. B.: Résultats fonctionnels dans 50 cas de kératoplastie avec quelques détails sur la technique opératoire, Schweiz. med. Wchnschr. **73**:1371-1374, 1943.

(4) disciform keratitis and (5) keratoconus with central opacity. They expressed the opinion that adherent leukoma with almost no anterior chamber and aphakia are unfavorable for transplantation.

II. Tectonic keratoplasty. Keratoplasty is indicated for reconstructive purposes in cases of descemetocele and staphyloma of the cornea.

III. Prophylactic keratoplasty. Keratoplasty is indicated in certain cases of corneal ulcer with a tendency toward perforation.

IV. Therapeutic keratoplasty. Franceschetti[9] advocated keratoplasty as treatment for (1) relapsing keratitis, (2) epithelial (and parenchymatous) corneal degeneration with recurring erosion and (3) recurring scrofulous keratitis with superficial pannus.

In the symposium on corneal transplantation held by the American Academy of Ophthalmology and Otolaryngology in 1947, Paton[10] discussed the selection of cases for operation. He advised surgeons to be reluctant to perform this operation on (1) patients with less than 20/200 visual acuity who are well adjusted and self supporting, (2) one-eyed patients and (3) patients who might be improved by an optical iridectomy. Paton divided eyes destined for keratoplasty into six groups, as follows:

I. Eyes favorable for improvement of vision. (There must be no active corneal disease and no active infection of the conjunctiva, sclera or uveal tract. There must be no glaucoma and no vascularization of the cornea). This group includes eyes with (1) central nebulous opacity, (2) blood staining of the cornea and (3) conical cornea.

II. Eyes partially favorable for improvement of vision. This group includes eyes with (1) some corneal vascularization, such as old interstitial keratitis; (2) central corneal opacities that are not too dense and with some surrounding clear cornea; (3) adherent leukoma, if the adhesions are first destroyed; (4) corneal dystrophy (Groenouw or Salzmann type); (5) fatty degeneration of the cornea, and (6) band-shaped degeneration of the cornea.

III. Eyes unfavorable for improvement of vision. This group includes eyes with (1) pronounced nystagmus, (2) dense scarring of the cornea from powder burns, (3) lime burns, (4) hypersensitivity from any cause and (5) old trachoma.

IV. Eyes favorable only for cosmetic improvement. Eyes in which tattooing was formerly employed may be benefited by corneal grafting.

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9. Franceschetti, A.: Nouvelles indications de la greffe cornéenne, Ophthalmologica **101**:247-249, 1940

10. Paton, R. T.: Symposium: Corneal Transplantation: I. Selection of Cases, Tr. Am. Acad. Ophth. **52**:312-316, 1948.

V. Eyes with descemetocele. There is, according to Paton, no treatment for this condition more favorable than corneal transplantation.

VI. Eyes for which preliminary operation or treatment is necessary. This category includes eyes with (1) extensive anterior synechiae and (2) glaucoma.

Comment.—The differences of opinion revealed in the preceding paragraphs offer ample testimony that the prognosis in corneal transplantation is still a moot question. This confusion is the result of several factors. One is the inclusion of cases in which the prognosis was hopeless from the beginning, as a result of amblyopia ex anopsia, pathologic conditions of the fundus or unsuitability of the patient; the characteristics of the corneal lesion have no demonstrable effect on the visual results in such cases. Another factor is the inclusion of operations performed for cosmetic purposes; these transplantations (contraindicated in any case) should certainly be considered separately, because the results have no meaning in an analysis of the visual results of corneal transplantation. A number of opinions have been expressed concerning the suitability for corneal transplantation of various uncommon corneal lesions, regardless of the fact that opinions based on the results in 1 or 2 cases of a certain lesion carry no weight. None of the surgeons mentioned here have divided their series of cases into diagnostic groups; consequently, the significance of their opinions concerning these rare lesions cannot be estimated. The opinions in the literature concerning the prognosis in corneal transplantation are also devaluated by the general exuberance found in the reports of this operation. Finally, it was pointed out in the previous paper [1] that there is no agreement concerning the standard of success in corneal transplantation, inasmuch as most surgeons have considered a clear graft adequate evidence of a successful result. However, I reiterate that a clear corneal graft with no improvement in visual acuity cannot be considered a success in optical keratoplasty.

A majority of the surgeons mentioned here have agreed on the suitability of certain lesions for corneal transplantation. The lesions generally considered favorable are: (1) interstitial keratitis, (2) keratoconus, (3) hereditary corneal degenerations, (4) small corneal opacities with little or no vascularization and (5) large corneal opacities, if superficial and attended by little or no vascularization. The conditions generally considered unfavorable for keratoplasty include: (1) aphakia, (2) glaucoma, (3) staphyloma of the cornea, (4) Fuchs's epithelial dystrophy, (5) extensive anterior synechiae, (6) extensive leukomas with heavy vascularization and (7) total leukomas with no transparent cornea. Each of these unfavorable conditions was considered a contraindication by at least one author, a finding which sug-

gests that one of the problems in establishing the basis for prognosis in corneal transplantation is the decision whether these conditions are merely unfavorable or are true contraindications. The suitability for operation of eyes with glaucoma furnishes a good example of this problem. Elschnig stated that the glaucomatous state was unfavorable, whereas Filatov said that keratoplasty was contraindicated in the presence of glaucoma. Thomas did not discuss glaucoma. Castroviejo first said that increased intraocular tension was unfavorable but did not mention it in his more recent classification. Paton expressed the opinion that preliminary operation is necessary before transplantation in cases of glaucoma. There is also a difference of opinion concerning the prognosis for corneal leukomas associated with small anterior synechiae, some surgeons believing that small synechiae can be broken at the time of transplantation and others asserting that a preliminary operation is needed to sever the synechiae. Other conditions about which there is disagreement are (1) leukomas with calcareous degeneration, (2) band-shaped degeneration of the cornea and (3) fatty degeneration of the cornea. The majority of surgeons agree that the operation should not be performed on patients who obviously cannot be expected to cooperate after operation, and that there is no hope of success in eyes with an adherent leukoma and little or no anterior chamber. In addition to these indications for optical keratoplasty, some surgeons advise tectonic corneal transplantation for descemetocele and for staphyloma of the cornea. Other surgeons recommend cosmetic corneal transplantation for unsightly corneal scars, instead of a tattooing operation. Prophylactic keratoplasty has been recommended by Löhlein [11] in certain cases of corneal ulcer that threaten to perforate. Therapeutic transplantation has been advised by Franceschetti [9] for chronic forms of keratitis that are resistant to other forms of therapy.

PRESENT STUDY

In the initial report [1] on this series of operations, the visual and cosmetic results of 165 corneal transplantations performed at the Institute of Ophthalmology from 1933 to 1948 were discussed and analyzed. At that time, results were given for the entire series without any selection of cases. This was done because of an obviously increasing need for this information, largely the result of the sensational publicity surrounding the operation. Particular attention was devoted to the functional result; preoperative and postoperative visual acuity and refraction were included. I criticized the symposium on corneal transplantation held by the American Academy of Ophthalmology

11. Löhlein, W.: Keratoplastik, in Zeitfragen der Augenheilkunde, Stuttgart, F. Enke, 1938, p. 405.

and Otolaryngology in which the results of this operation, as performed in seven leading ophthalmologic clinics, were greatly improved on paper by the indiscriminate exclusion of unfavorable cases. When over one third of a series of operative cases is excluded from a report because of unfavorable conditions existing before operation, this becomes an indictment, not of the operation, but of the physicians reporting the operation. I agree that in any new surgical procedure operations will be performed in unfavorable cases, when it is necessary to ascertain postoperative results under varying conditions. This is due to "last straw" demands of the patient and family, to enthusiasm of the surgeon and to the evanescent idea in the minds of both parties that a startling new procedure can effect the impossible. It is impossible, however, for a technically successful corneal transplantation to restore vision lost through glaucoma, amblyopia ex anopsia or chorioretinal lesions. In this series of operations, which includes most of the early corneal transplantations performed in this country, there are some cases in which the clinical record before operation contained information that refuted any possibility of postoperative improvement in visual acuity. The inclusion of such operations in an analysis of preoperative factors can only lead to confusion. Therefore these cases have been excluded from the present evaluation, even though they were included in the analysis of the results in an unselected series of operations.

Data in 9 cases were excluded from the present discussion of the indications for corneal transplantation because of pathologic conditions existing before the corneal grafting. The diagnosis and visual result in these 9 cases were as follows:

Series No.[12]	Diagnosis	Visual Result
44	Central chorioretinitis	Unchanged
82	Amblyopia ex anopsia	Unchanged
86	Amblyopia ex anopsia	Unchanged
87	Amblyopia ex apopsia	Unchanged
97	Amblyopia ex anopsia	Unchanged
101	Pannus degenerativus Psychopathic personality	Loss of all vision
102	Central chorioretinitis	Unchanged
120	Amblyopia ex anopsia	Unchanged
133	Amblyopia ex anopsia	Unchanged

In 6 cases amblyopia ex anopsia was the responsible factor; in all 6 cases this difficulty was incurred before the age of 6 years. In 2 other cases central chorioretinal scars were found, in 1 case the eye having high myopia. Psychopathic personality, degenerative pannus, cataract and a preglaucomatous state were considered sufficient to contraindicate

12. The serial numbers used here and in the following tables refer to the same operations as the numbers in the tables of the previous paper.[1]

operation in the remaining case; this patient was impossible to control after operation and was transferred to a psychiatric institution. The visual results in these 9 cases confirmed the poor prognosis assigned to them; there was no significant change in visual acuity in 8 cases, and loss of acuity followed operation in 1 case. The exclusion of these 9 leaves 156 available for study of the effect of various preoperative factors on the success of corneal transplantation. It should be reemphasized that many of these operations were performed when this procedure was "new," at least in this country. Therefore, it is more than likely that there are data on other operations that should be excluded if more information were available. For example, there may well have been additional instances of amblyopia ex anopsia, but the diagnosis of this condition is difficult to substantiate in the adult with other pathologic conditions of the eye and a poor memory, and has been included in this report only when it was found in the patient's record. For this

TABLE 1.—*Visual Results in the Entire Series Compared with Results in Its Component Group*

Operation Groups	Number of Operations	Final Visual Result		
		Improved	Unchanged	Decreased
Operations with preoperative contraindications.	9	..	8	1
Primary (initial) corneal transplantations.....	122	30	57	43
Secondary corneal transplantations.....	34	2	21	11
Total series of operations (without any selection).....	165	32	86	57

reason, the results in this series of operations are probably considerably less favorable than can be anticipated in future series.

In addition to the exclusion of the 9 cases in which there was no possibility of improving visual acuity, the 34 cases of secondary corneal transplantation are also considered separately in this analysis. To include these complicated operations would only tend to invalidate the conclusions of the whole study because of the false significance that would be attached to various factors in eyes undergoing more than one transplantation. Besides repetition of these preoperative factors, the inclusion of secondary corneal transplantations would confuse the result, since the postoperative complications of the primary operation become preoperative complications for the secondary operation. Furthermore, the majority of the eyes undergoing multiple corneal transplantations showed extensive vascularization and opacification of the cornea, and many of the eyes had secondary glaucoma. On the whole, the pathologic changes in these eyes showed little resemblance to those in the remainder of this series. Therefore the secondary corneal transplantations are better considered separately. In table 1 the results in the whole series of 165 operations are compared with the results in the three separate

No.	Size of Opacity (Coverage of Cornea)	Vascularization	Preoperative Complications Previous Operations	Age	Sex	Race	Prognosis	Type of Graft	Size of Graft, Mm.	Visual Result (Final Vision)
				I. Keratoconus						
1	Under ⅓	None	None	30	M	W	.....	Square	...	Improved
2	Under ⅓	None	None	30	M	W	.....	Circular	4.5	Unchanged
3	Under ⅓	None	None	40	M	W	Very favorable	Square	4.5	Unchanged
4	Under ⅓	None	None	11	M	N	Very favorable	Square	4.5	Unchanged
5	Under ⅓	None	Optical iridectomy	38	M	W	Favorable	Square	...	Improved
6	Under ⅓	None	None	24	M	W	Very favorable	Square	5	Loss of vision
7	Under ⅓	None	None	12	M	N	Very favorable	Square	5.5	Loss of vision
8	Under ⅓	None	Vernal conjunctivitis	23	M	W	Very favorable	Square	...	Improved
9	Under ⅓	None	Vernal conjunctivitis	22	M	W	Very favorable	Square	6.5	Loss of vision
10	Under ⅓	None	None	30	M	W	Very favorable	Square	6	Loss of vision
11	None	None	None	31	M	W	Favorable	Square	5.5	Improved
12	.....	.....	None	21	M	W	Very favorable	Square	5	Loss of vision
13	Under ⅓	None	None	29	M	W	Very favorable	Square	5	Unchanged
14	None	None	None	32	M	W	Favorable	Square	5.5	Unchanged
15	Under ⅓	None	None	27	F	N	.....	Square	5.5	Unchanged
16	.....	.....	None	40	F	N	Favorable	Square	5	Loss of vision
17	Under ⅓	None	None	29	M	W	Favorable	Square	5	Improved
18	Under ⅓	None	None	30	F	N	Very favorable	Square	6	Improved
19	Under ⅓	None	None	41	F	W	Favorable	Square	5	Loss of vision
20	Under ⅓	None	None	21	M	W	Favorable	Square	5	Loss of vision
21	None	None	None	20	M	W	Very favorable	Square	5.5	Loss of vision
22	Under ⅓	Moderate	Optical iridectomy; electrodesiccation	45	F	W	Favorable	Square	6	Unchanged
23	Under ⅓	None	None	42	F	N	Favorable	Square	5	Unchanged
24	None	None	None	26	M	W	Very favorable	Square	6	Improved
25	Under ⅓	None	Exotropia	33	F	N	Favorable	Square	6	Loss of all vision
26	Under ⅓	.....	None	35	M	N	Very favorable	Square	6	Loss of vision
27	Under ⅓	None	None	44	F	W	Favorable	Square	6	Unchanged
28	None	None	None	25	F	N	Favorable	Square	6	Improved
29	Under ⅓	None	None	31	F	N	Favorable	Square	6	Unchanged
30	Under ⅓	None	None	31	F	N	Very favorable	Square	6	Improved
31	Under ⅓	None	None	21	M	W	Favorable	Square	5.5	Unchanged
32	Under ⅓	None	None	45	F	W	Favorable	Square	6	Unchanged
33	Under ⅓	None	None	27	M	W	Very favorable	Square	6	Loss of vision
34	Under ⅓	None	None	29	F	W	.....	Square	6	Unchanged
35	.....	Extensive	Optical iridectomy	19	F	N	.....	Square	5	Improved
				II. Corneal Dystrophies						
				A. Haab-Dimmer Type						
36	Over ⅓	None	None	32	F	W	Unfavorable	Square	5	Unchanged
37	Over ⅓	None	None	35	F	W	Favorable	Square	5.5	Loss of all vision
38	Over ⅓	None	Optical iridectomy	61	M	W	Favorable	Square	5	Improved
				B. Groenouw's Type						
39	Over ⅓	None	None	42	F	W	.....	Square	5.5	Improved
				C. Fuchs's Epithelial Type						
40	Over ⅓	.....	Curettage of cornea	55	M	W	Very favorable	Square	4.5	Loss of vision
				D. Unclassified Type						
41	Over ⅓	Moderate	None	44	M	W	Favorable	Square	5	Unchanged
42	Over ⅓	Little	Preliminary iridectomy	39	F	W	.....	Square	5	Unchanged
43	Entire	Little	Glaucoma; modified Lagrange operation	68	F	W	Unfavorable	Square	5.5	Loss of all vision
45	Over ⅓	None	None	33	F	W	Favorable	Square	6.5	Loss of vision
46	Over ⅓	None	None	34	F	N	Favorable	Square	5.5	Unchanged
47	Entire	None	None	20	M	W	Unfavorable	Circular	5.5	Unchanged
48	Over ⅓	None	None	50	F	W	Unfavorable	Circular	6.5	Unchanged
				III. Interstitial Keratitis						
49	Entire	Moderate	Optical iridectomy; tattooing of the cornea	60	M	W	.....	Square	4	Loss of all vision
50	Entire	Extensive	Two complete iridectomies	39	M	W	.....	Square	...	Loss of vision
51	Entire	Moderate	Anterior synechiae; preliminary iridectomy	25	M	W	.....	Square	..	Unchanged
52	Entire	Extensive	None	19	F	W	Unfavorable	Square	4.5	Unchanged
53	Entire	Extensive	None	19	F	W	Favorable	Square	4.5	Unchanged
54	Over ⅓	Moderate	None	28	F	W	Very favorable	Square	4.5	Improved
55	Over ⅓	Moderate	None	36	F	W	Very favorable	Circular	...	Loss of vision
56	Entire	Moderate	None	22	F	W	Favorable	Square	...	Loss of vision
57	Entire	Extensive	None	32	M	W	Favorable	Square	...	Loss of vision
58	Under ⅓	Moderate	None	24	M	W	Favorable	Square	...	Unchanged
59	Entire	Extensive	None	48	F	W	Favorable	Square	4.5	Loss of vision
60	Under ⅓	Moderate	None	24	M	W	Favorable	Square	5	Unchanged
61	Entire	.....	None	40	F	W	Favorable	Square	5.5	Unchanged
62	Over ⅓	Moderate	Optical iridectomy	27	M	W	Favorable	Square	4.5	Improved
63	Over ⅓	Moderate	None	27	M	W	Favorable	Square	4	Improved
64	Entire	Moderate	Preliminary iridectomy	58	M	W	Unfavorable	Square	4.5	Unchanged
65	Entire	Moderate	None	29	M	W	Favorable	Square	5	Unchanged
66	Entire	Extensive	None	15	F	N	Favorable	Square	5.5	Loss of vision
67	Entire	Extensive	None	36	F	W	Favorable	Circular	...	Unchanged
68	Entire	Extensive	Two preliminary iridectomies	28	F	W	Unfavorable	Square	5	Unchanged
69	Entire	Extensive	Cataractous changes	21	F	W	Favorable	Square	5	Unchanged

No.	Size of Opacity (Coverage of Cornea)	Vascularization	Preoperative Complications Previous Operations	Age	Sex	Race	Prognosis	Type of Graft	Size of Graft, Mm.	Visual Result (Final Vision)
				IV. Chemical Burns						
70	Entire	Moderate	None	40	M	W	.....	Square	5	Unchanged
71	Over ½	Extensive	Preliminary iridectomy	22	M	W	Favorable	Square	...	Unchanged
72	Entire	Extensive	Glaucoma	56	M	W	Unfavorable	Square	...	Loss of all vision
73	Entire	Extensive	None	32	M	W	.....	Square	...	Unchanged
74	Entire	Extensive	None	23	M	W	Favorable	Square	4	Unchanged
75	Entire	Extensive	None	26	M	W	Favorable	Square	4	Unchanged
76	Entire	Extensive	Preliminary iridectomy	26	M	W	.....	Square	...	Unchanged
77	Entire	Extensive	Multiple peritomies	31	M	W	Favorable	Square	4.5	Loss of vision
78	Entire	Extensive	Multiple peritomies	31	M	W	Favorable	Square	4.5	Unchanged
				V. Traumatic Scars						
79	Entire	.....	Extensive anterior synechia; ectasia of the cornea; secondary glaucoma Preliminary iridectomy; excision of staphyloma	29	F	W	.....	Square	5	Unchanged
80	Under ½	Extensive	Extensive anterior synechia	55	F	W	Favorable	Square	...	Loss of vision
81	Under ½	.....	Anterior synechiae	29	M	W	Unfavorable	Square	...	Unchanged
82	Under ½	Moderate	Superficial keratectomy	41	M	W	Very favorable	Square	5	Improved
84	Under ½	.....	None	26	M	W	Favorable	Square	5.5	Loss of vision
				VI. Postinflammatory Scars						
85	Entire	Extensive	None	55	F	W	Favorable	Square	5	Unchanged
88	Over ½	Moderate	Anterior synechia Preliminary iridectomy; cyclodialysis; excision of corneal staphyloma	24	M	W	.....	Square	...	Unchanged
89	Under ½	Moderate	None	35	M	W	.....	Square	...	Loss of vision
90	Under ½	Little	None	45	M	W	Very favorable	Square	4.5	Unchanged
91	Over ½	.....	Conjunctival flap	26	F	W	Unfavorable	Square	5.5	Unchanged
92	Under ½	Moderate	Secondary glaucoma Multiple paracenteses	20	M	W	Very favorable	Square	4.5	Unchanged
93	Under ½	.....	None	12	F	W	Very favorable	Square	4.5	Improved
94	Entire	Moderate	None	29	F	W	Favorable	Square	4.5	Loss of all vision
95	Over ½	Moderate	Secondary glaucoma	24	F	W	Unfavorable	Square	6	Loss of all vision
96	Under ½	.....	None	5	M	W	Very favorable	Square	4.5	Unchanged
98	Entire	Moderate	None	13	F	N	Very favorable	Square	4.5	Loss of all vision
99	Under ½	.....	None	18	F	W	Very favorable	Square	...	Loss of vision
100	Over ½	Moderate	None	23	M	W	Favorable	Square	5.5	Loss of vision
103	Entire	Extensive	None	37	F	W	.....	Square	5	Unchanged
104	Entire	Moderate	Superficial keratectomy	35	F	W	.....	Square	5	Unchanged
105	Under ½	Little	Electrocoagulation of corneal blood vessels	27	F	W	Favorable	Square	5.5	Loss of vision
106	Over ½	.....	None	22	F	W	Favorable	Circular	6.5	Improved
				VII. Scars of Unknown Origin						
107	Entire	Moderate	Preliminary iridectomy	58	F	W	Favorable	Square	4	Unchanged
108	Entire	Moderate	None	58	F	W	Favorable	Square	4	Unchanged
109	Entire	Extensive	Anterior polar cataract Preliminary iridectomy	71	M	W	Favorable	Square	...	Unchanged
110	Entire	Extensive	None	60	M	W	Favorable	Square	...	Unchanged
111	Entire	Extensive	Extensive anterior synechia; secondary glaucoma Cyclodialysis; complete iridectomy	74	M	W	.....	Square	...	Loss of all vision
112	Entire	Extensive	None	60	M	W	Favorable	Square	...	Loss of vision
113	Over ½	Moderate	None	41	F	W	Unfavorable	Square	5	Unchanged
114	Over ½	Moderate	Anterior synechia	41	F	W	Unfavorable	Square	5	Unchanged
115	Under ½	Little	None	48	F	N	Favorable	Square	4.5	Improved
116	Under ½	None	None	44	F	W	Very favorable	Square	...	Unchanged
117	Entire	Extensive	None	41	F	W	.....	Square	4.5	Loss of vision
118	Under ½	Little	None	48	F	N	Favorable	Circular	4.5	Improved
119	Over ½	Moderate	None	60	M	W	Favorable	Square	4.5	Loss of vision
121	Entire	None	None	44	M	W	Very favorable	Square	4.5	Loss of vision
122	Under ½	None	None	45	M	W	.....	Square	5.5	Loss of all vision
123	Over ½	.....	None	28	F	N	Favorable	Square	4.5	Unchanged
124	Over ½	Moderate	None	35	F	W	.....	Square	6	Unchanged
125	Entire	Extensive	Posterior synechiae Preliminary iridectomy	56	F	W	.....	Square	5	Loss of vision
126	Over ½	Moderate	Superficial keratectomy	20	M	W	.....	Circular	4.5	Loss of vision
127	Over ½	Moderate	Superficial keratectomy	70	M	W	.....	Square	...	Loss of vision
128	Over ½	Little	Posterior synechiae; cataract Preliminary iridectomy	60	F	W	Unfavorable	Square	4.5	Unchanged
129	None	None	None	20	F	W	.....	Square	6	Loss of vision
130	Entire	None	None	18	M	W	.....	Circular	6	Loss of all vision

groups. The significant changes resulting from the exclusion of these two groups of operations are (1) a reduction in the number of cases with loss of light perception in the primary corneal transplantations, and (2) a relative increase in the number of successful results in the group of primary operations.

PRIMARY CORNEAL TRANSPLANTATIONS

In the attempt to assess the findings in these 122 eyes before corneal transplantation, the clinical records have again been reviewed and information on the following points has been noted: (1) diagnosis, (2) size of the corneal opacity, (3) degree of corneal vascularization, (4) preoperative complications and operations, (5) age, (6) sex, (7) race and (8) preoperative prognosis. In addition, certain factors pertaining to the operative procedure were analyzed for their possible effect on the final visual result; these included (1) type of operation, (2) size of graft, (3) surgeon and (4) year in which the operation was performed. A tabulation of most of these factors in the 122 cases of primary corneal transplantations in this series is found in table 2. The cases are again arranged in diagnostic groups, and the diagnoses are the same as those given in the preceding paper.[1] In discussion of the characteristics of the cornea before operation, the exact words found in the clinical record are employed as much as possible. The terms "none," "under ½," "over ½," and "entire" are used to describe the size of the corneal opacities. Some opacities were described as "central," but this was not considered significantly different from the expression "under ½." In respect to vascularity of the cornea, the terms "none," "little," "moderate" and "extensive" were most common in the clinical records and appear well suited to this analysis. Preoperative complications and operations are tabulated together, to conserve space and because they were so often linked together, the complications being the occasion of the operation. Age, sex and race require no further explanation. The preoperative prognosis is given according to the schema of Castroviejo, using the terms "very favorable," "less favorable," "unfavorable" and "operation contraindicated." The type of operation and the size of graft are stated exactly as recorded. The name of the surgeon is not included, for obvious reasons. The year of the operation was given in the initial paper [1] and so need not be repeated. The final column in table 2 contains an evaluation of the visual results, based on the standards described in the preceding paper [1] on results of the operation. Whenever any of this information was not found in the patient's record, it was considered "unknown" and was so indicated in table 2 by a dieresis.

Diagnosis.—The relation of the diagnosis of the corneal lesion to the postoperative visual result in these cases of primary corneal trans-

plantation is shown in table 3. It is quite evident that the results in each diagnostic group differ very little from the results in the same groups in the analysis of the entire series (table 11 of the preceding report [1]). The best results are still found in cases of keratoconus and the poorest in cases of chemical burns. When these two diagnostic groups are excluded, the incidence of successful operations is fairly constant in the remaining diagnostic groups; this suggests that diagnosis alone is probably an unreliable factor on which to base prognosis before operation.

An interesting finding in this survey is the fact that none of the corneal transplantations performed on eyes with a degenerative process of the cornea resulted in improvement in vision. Six such operations were performed in this series: in cases 40 and 150, performed on a

TABLE 3.—*Relation of Diagnosis to Final Visual Result in 122 Primary Corneal Transplantations*

Diagnosis	Number of Operations	Final Visual Result		
		Improved	Unchanged	Decreased
Keratoconus	55	30	13	12
Corneal dystrophies	12	2	6	4
Interstitial keratitis	21	3	11	7
Chemical burns	9	..	7	2
Traumatic scars	8	1	2	5
Postinflammatory scars	17	2	8	7
Scars of unknown etiology	20	2	10	11
Totals	122	20	57	45

cornea with Fuchs's epithelial dystrophy; in cases 126, 127 and 155, performed on eyes with primary fatty degeneration of the cornea, and in case 128, performed on an eye with band keratitis. Since a technically successful graft in these eyes will be surrounded after operation by degenerative corneal tissue and will be dependent on this diseased tissue for the transmission of its nutritional substances, it is logical to anticipate a poor visual result in cases of corneal degenerations. Although the number of cases of a corneal degenerative process in this series is not large enough to substantiate this assumption, it is likely that future statistics may prove that corneal transplantation is contraindicated in the corneal degenerations.

Size of Opacity.—The relation of the size of the corneal opacity to the final visual result is shown in table 4. Perusal of this table shows that the smaller the corneal opacity, the better the visual result. In eyes with no corneal opacification, 1 of 2 operations led to improvement in vision. Approximately 1 of 4 operations on eyes with opacification of less than one-half the cornea was successful, and the result in about 1 of 5 eyes with a corneal opacity larger than one-half the cornea was

good. None of the operations on eyes with opacification of the entire cornea was successful. The fact that half the operations on corneas without an opacity were successful may be misleading because of the small number of such cases. Nevertheless, this tabulation shows that in this group of cases with a recorded corneal opacity the visual result improved in inverse proportion to the size of the opacity. It appears significant that the visual results in eyes with an opacity covering over one-half the cornea were almost as good as the results in the eyes with

TABLE 4.—*Relation of Size of Corneal Opacity to Final Visual Result in 122 Primary Corneal Transplantations*

Size of Opacity in Relation to the Cornea	Number of Operations	Final Visual Result		
		Improved	Unchanged	Decreased
None	6	3	1	2
Under one-half	44	10	19	15
Over one-half	28	6	13	9
Entire	41	..	24	17
Unknown	3	1	..	2
Totals	122	20	57	45

TABLE 5.—*Relation of Corneal Vascularization to Final Visual Result in 122 Primary Corneal Transplantations*

Extent of Corneal Vascularization	Number of Operations	Final Visual Result		
		Improved	Unchanged	Decreased
None	43	11	17	15
Little	7	2	3	2
Moderate	31	4	16	11
Extensive	27	1	15	11
Unknown	14	2	6	6
Totals	122	20	57	45

an opacity smaller than one-half the cornea. This suggests the possibility that the size of the opacity is not important so long as enough clear cornea surrounds the graft. This idea is further substantiated by the poor results in the eyes with opacification of the entire cornea.

Vascularization.—The relation of corneal vascularization to the visual results of corneal transplantation is presented in table 5, which shows that the best results were obtained in eyes with little or no vascularization of the cornea. Approximately 1 of 4 operations on eyes with little or no corneal vascularization was followed by improvement in visual acuity; about 1 in 8 operations on eyes with moderate corneal vascularization was successful, and only 1 of 27 operations on eyes with extensive corneal vascularization resulted in improved vision. It appears sig-

nificant that the results in eyes with a little corneal vascularization were as good as the results in the group of eyes without any vascularization of the cornea. This suggests that slight corneal vascularity may even be a favorable factor in corneal transplantation. However, the significance of this supposition is weakened by the small number of corneas with little corneal vascularization in which the transplantation was done. It is significant that only 1 of 27 operations was successful on eyes with extensive vascularization of the cornea. Experience with this series of operations, then, leads to the conclusion that successful results in corneal transplantation increase in inverse proportion to the amount of corneal vascularization.

Preoperative Complications.—In addition to the corneal lesion, other ocular pathologic processes were present before operation in 19 of the 122 eyes undergoing primary corneal transplantation. These complications may be seen in table 2. Anterior synechiae were present before operation in 7 eyes; none of the operations on these eyes resulted in improvement in vision. Cataractous changes were found in 3 eyes before operation. The diagnosis of exotropia was made before operation in 1 case, and an unsuccessful transplantation was performed on the deviating eye; the strabismus began during adult life and so cannot be indicated as the cause of the loss of vision. Glaucoma was present in 7 eyes at the time of corneal transplantation; none of these operations resulted in improved vision. Posterior synechiae were seen in 2 eyes before operation and staphyloma of the cornea in 2 other eyes; none of these 4 eyes achieved improved visual acuity after operation. Vernal conjunctivitis was diagnosed in 2 eyes (of the same patient), with postoperative improvement in visual acuity in one eye and loss of visual acuity in the other. In 4 cases, more than one complication occurred in the same eye. Anterior synechia, corneal staphyloma and glaucoma occurred in one eye; anterior synechia and corneal staphyloma in the second eye; anterior synechia and glaucoma, in the third eye, and cataractous changes and posterior synechiae, in the fourth eye. The final postoperative visual results in the 19 eyes with preoperative complications were as follows: improved visual acuity, 1 eye; no significant change in visual acuity, 10 eyes; decreased visual acuity, 8 eyes. The most pertinent finding here is the fact that none of the 12 eyes with anterior synechiae and/or glaucoma were improved by corneal transplantation.

Preliminary Operations.—Thirty-six preliminary operations were performed on 30 eyes of this series of 122 eyes with primary corneal transplantations; the data on these 30 eyes can be found in table 2. In an effort to reduce the amount of corneal scar tissue, corneal curettage was performed on 1 eye and superficial keratectomy on 4 other eyes. In

an attempt to reduce the intraocular tension, cyclodialysis was performed on 2 eyes, a modified Lagrange operation on 1 eye, and multiple paracenteses, on another eye. To reduce the corneal vascularity, electrocoagulation of the corneal blood vessels was done in 2 eyes, and peritomy in 2 other eyes. Excision of a corneal staphyloma was performed in 2 eyes. Tattooing of the cornea to hide a disfiguring scar had been performed on 1 eye. To improve visual acuity, optical iridectomy had been done in 6 eyes prior to corneal transplantation. Preliminary iridectomy was performed on 14 eyes in this group. More than one preliminary operation was performed on 5 of the 30 eyes. Electrocoagulation of corneal blood vessels and optical iridectomy were done on 1 eye, with no change in vision after the ensuing corneal transplantation. On a second eye, optical iridectomy and tattooing of the cornea were done before a transplantation that resulted in loss of vision. Another eye had excision of a corneal staphyloma and preliminary iridectomy before the corneal graft, which was unsuccessful. One eye had cyclodialysis, excision of a corneal staphyloma and preliminary iridectomy before corneal transplantation that resulted in no significant change in vision. The fifth eye had cyclodialysis and a preliminary iridectomy before corneal transplantation, which was unsuccessful.

The significance of the effect of these preliminary operations on the results of corneal transplantation is difficult to estimate because of the small number of operations of each type. None of the 4 operations for glaucoma, none of the 4 operations performed to reduce corneal vascularity and none of the 14 preliminary iridectomies were followed by successful corneal transplantations. Likewise, neither of the 2 excisions of corneal staphyloma was followed by a successful graft. One of the 4 superficial keratectomies performed to reduce the amount of corneal scarring was followed by a successful corneal transplantation, and 4 of the 6 eyes with optical iridectomies achieved improved vision after corneal grafting. The importance of the last fact is difficult to ascertain. It suggests that iridectomy in a healthy eye (optical iridectomy) is an advantage before corneal transplantation, whereas iridectomy performed for another pathologic condition (preliminary iridectomy) is not similarly favorable. With the exception of the 4 optical iridectomies and 1 superficial keratectomy, none of the 36 preliminary operations exerted any demonstrable beneficial effect on the results in this series of primary corneal transplantations.

Age, Sex and Race.—The relation of the patient's age, sex and race to the visual results of corneal transplantation in this series of primary operations can be seen in table 2.

1. Age: The youngest patient was 5 and the oldest was 69 years of age. More than one-half the patients were in the third and fourth decades of life. The distribution of successful results was fairly constant for all age groups, about 1 of 6 patients obtaining improvement in visual acuity. There is no discernible correlation between the age of the patient and the operative result.

2. Sex: Approximately one-half the patients fall into each category, 63 operations being performed on males and 59 on females. The successful visual results were evenly divided, 10 persons of each sex obtaining improved vision. Apparently, the sex of the patient had no effect on the outcome in this series of corneal transplantations.

3. Race: Eighteen of the corneal transplantations in this group were performed on Negroes and the remainder on white persons. Division

TABLE 6.— *Relation of Preoperative Prognosis to Postoperative Visual Acuity in 122 Primary Corneal Transplantations*

Prognosis Before Operation	Number of Operations	Final Visual Result		
		Improved	Unchanged	Decreased
Very favorable	27	7	7	13
Favorable	54	10	26	18
Unfavorable	14	..	11	3
Operation contraindicated	..	..	..	..
Unknown	27	3	13	11
Totals	122	20	57	45

of the series on the basis of these two racial groups reveals a surprising difference in the results. Of the series of transplantations on Negroes, one third resulted in improved vision, one third in no significant change and one third in loss of vision. Whether or not the excellent behavior of the average Negro patient in the hospital is a contributing factor in this disproportion is an interesting subject for speculation. At any rate, the visual results in this series of corneal transplantations were considerably better in Negroes than in white patients.

Preoperative Prognosis.—The relation of the prognosis before corneal transplantation to the postoperative visual result is shown in table 6. Of the 27 eyes designated as very favorable, improved visual acuity occurred in 7, no significant change in acuity in 7 eyes and a decrease in visual acuity in 13 eyes. Of the 54 eyes designated as favorable, visual acuity was improved in 10, not significantly changed in 26 eyes and decreased in 18 eyes. Of the 14 eyes with an unfavorable condition, none achieved improved vision; visual acuity was not significantly changed in 11 and was decreased in 3. According to the patient's records, corneal transplantation was not contraindicated in

any of the 122 cases in this series. The prognosis was not stated in the records of 27 patients; operation resulted in improved visual acuity in 3 of these patients, in no significant change in acuity in 13 and in loss of vision in 11. The first, and most obvious, conclusion to be drawn from this survey of the prognosis in corneal transplantation is that none of the eyes in this series of operations were "very favorable" for operation; for the 27 so classified, the results for less than one fourth were successful, while over three fourths showed no improvement in visual acuity. Also significant is the high percentage of eyes in this category in which operation resulted in loss of vision; in 13 of the 27 eyes designated as "very favorable" loss of vision resulted. The conclusion is inevitable, therefore, that with present knowledge of corneal transplantation no eye should be classified as "very favorable" for operation. In the favorable group (called less favorable by Castroviejo) of 54 eyes, 10 achieved improved visual acuity, while 44 were not improved by corneal transplantation. On the assumption that the 27 eyes considered "very favorable" before operation should at least be considered to have had a favorable prognosis, these two groups have been combined and the results analyzed together; the result is a group of 81 eyes regarded as favorable for corneal transplantation. In 17 of this group operation resulted in improvement in visual acuity. Thirty-three eyes showed no significant change in acuity, and 31 eyes suffered loss of vision. Comparison of these results with those for the entire group of 122 eyes with primary transplantations reveals that there is no statistically significant difference between the results for the favorable eyes and the results for the whole group, regardless of the preoperative prognosis. Finally, then, one must conclude that the classification for prognosis set forth by Castroviejo[7] shows little or no correlation with the visual results of corneal transplantation in this series.

Other Factors in Corneal Transplantation.—Certain other factors, pertaining not to the patient's eye but to the operative procedure, were analyzed for possible effect on the results of corneal transplantation. These factors included type of operation, size of graft, surgeon and year in which the operation was performed. It was intended to include operative complications in this discussion, but almost none occurred in this series. During one operation (case 85), there was trauma to the lens, and cataractous changes followed. In another operation (case 33), the graft was cut too large for the window and had to be trimmed to size.

Type of Operation: In this series only one type of keratoplasty was performed—partial, penetrating transplantation. The misleading term "partial" refers to the size of the graft, not to its depth; this nomenclature is confusing, for partial grafts are easily confused with lamellar, or non-

penetrating, corneal grafts. In this series of partial, penetrating keratoplasties two forms of grafts were employed, namely, square and circular. In the large majority of these operations the square type was used, there being only 9 circular transplants. The visual results in these two groups did not differ significantly.

Size of Graft: The diameter of the graft in this series of operations varied from 4 to 6.5 mm. The size of the graft in 25 records was not stated. In general, the highest incidence of successful results was obtained with the grafts of 6 mm. or more. The number of operations employing grafts of the various sizes, however, was not great enough to permit any definite conclusions.

Surgeon: The 122 primary corneal transplantations in this series were performed by sixteen surgeons. Ten men performed only a single operation, and only three men did over ten transplantations. No one achieved results significantly different from the figures for the entire series.

Date of Operation: The visual results in this series of corneal transplantations were tabulated according to year of operation,[13] from 1933 to 1948, for the purpose of ascertaining any change in results with increasing experience. There were no successful results in the 23 operations performed in the four year period from 1933 to 1936, inclusive. There were 7 successful grafts in the series of 35 operations performed from 1937 to 1940. Improved vision followed 5 of the 22 operations performed from 1941 to 1944 and 8 of the 42 operations performed from January 1945 to May 1948. Except for the first four years of this period, there has been no important change in the incidence of successful visual results in this series of corneal transplants over a period of sixteen years. The poor results of the first four years is very likely explained by the type of lesion found in these early cases.

Comment.—Inasmuch as this series of corneal transplantations is one of the largest reported to date, the pertinent data are of considerable interest. The various findings that were analyzed fall under three heads: (1) factors showing no demonstrable relation to the final result, (2) factors showing a definite correlation with the final result and (3) factors of undeterminable significance. In this series of grafts, the following factors showed no significant effect on the final visual result: (1) diagnosis, (2) age, (3) sex, (4) preoperative prognosis, (5) type of operation, (6) size of the graft, (7) identity of the surgeon and (8) year in which the operation was performed. Two surprising developments were (1) the slight relation of diagnosis to the operative result, and (2) the absence of correlation between the preoperative prognosis

13. This information was presented in the tables of the initial report.[1]

and the final result. Only three preoperative features of the eyes in this series showed a definite relation to the final visual result: (1) extent of corneal opacification, (2) degree of corneal vascularization and (3) presence of other pathologic condition of the eye. The significance of two factors was indefinite: (1) preliminary operations and (2) race. The effect of preliminary operation depends on many unrelated factors, and it is difficult to correlate them. The only definitive statement that can be made concerning the effect of preliminary operations on the eyes in this series is that they were generally unsuccessful. With regard to race, the results were better in Negro than in white patients, but the number of Negroes was not large enough to make this finding significant.

On the other hand, a definite correlation can be seen between the final result and the extent of corneal opacification, degree of corneal vascularization and presence of other ocular complications. Cursory examination of the facts reveals that the visual results improved in inverse proportion to the size of the corneal opacity. However, more speculative examination of the data suggests that the actual size of the opacity may not be important so long as the graft is surrounded, or nearly surrounded, by clear cornea after operation. With regard to corneal vascularity, the final results again appeared to improve inversely with the degree of vascularization. It may be significant, however, that the results in eyes with little corneal vascularization were as good as the results in eyes with no corneal vascularity. Much more significant, however, is the fact that of the eyes with additional ocular complications, none with anterior synechiae and/or glaucoma attained improvement in vision. These various findings suggest that the basis for prognosis in this operation should depend on the presence or absence of these pathologic features, and that a simplified schema for prognosis might replace the present list of diagnosis with an individual prognosis for each condition. In some instances, such as keratoconus or chemical burns, the two classifications would coincide, because the benign nature of the corneal lesions makes keratoconus favorable for keratoplasty, whereas the severity of the corneal lesions from chemical burns is probably a contraindication to the operation.

In an attempt to simplify the prognosis in corneal transplantation according to the findings already discussed, the following schema is offered:

Favorable conditions

1. Small corneal scars that can be encompassed by a graft
2. Large superficial corneal scars in corneas in which the graft will be surrounded by normal corneal tissue posteriorly

3. Little or no corneal vascularization
4. Absence of other ocular pathologic disease

Unfavorable conditions

1. Total, or nearly total, corneal opacification
2. Extensive corneal vascularization
3. Presence of other ocular pathologic condition, associated with the corneal lesion
4. Degenerative processes of the cornea, such as: Fuchs's epithelial dystrophy, band keratitis, calcareous degeneration and primary fatty degeneration (possibly these degenerations should fall in the contraindicated group)

Contraindications

1. Glaucoma
2. Adherent leukoma

It can be anticipated with considerable certainty that this simplified classification for prognosis will be rejected by many surgeons because it does not include a number of the usually discussed conditions. It will be argued that this operation is not feasible in children or in other uncooperative patients. This is often true, but it is also true of many other operations on such patients; general factors of this kind, however, pertain to general surgical judgment and are not specific contraindications to the operation. It is also commonly stated that corneal transplantation is contraindicated in cases of aphakia, while actually the operation is merely more difficult in aphakic eyes. Another commonly expressed opinion is that eyes with adherent leukoma are favorable for corneal transplantation provided the adhesions to the iris are broken in a preliminary operation. This may be true, but those who have attempted to disrupt anterior synechiae know that it is not a simple task. Therefore, it would appear that an eye with an adherent leukoma should be considered unfavorable for keratoplasty until the iris has actually been freed from the cornea, at which time it is no longer an eye with an adherent leukoma. Likewise, it is frequently stated that eyes with glaucoma are favorable for transplantation provided the intraocular tension is first lowered by an operation for glaucoma. This is admittedly true, but then the eye is no longer glaucomatous. In such cases, it is well to remember the difficulty encountered in normalizing the intraocular tension in eyes with stubborn secondary glaucoma. Some have said that corneal transplantation is indicated for staphyloma of the cornea; in this instance, the burden of proof must remain with those who profess to believe this. A number of surgeons enthusiastically advise keratoplasty as the ideal treatment for descemetocele, but the results of transplantation to date scarcely warrant this form of therapy. One of the main points of dissension in this discussion will be the suitability for corneal transplantation of eyes with adherent leukoma or

secondary glaucoma. If these conditions were easily correctable, one might agree that these eyes are favorable for keratoplasty, but the obstinancy with which these conditions persist in spite of surgical intervention precludes this assumption.

It becomes evident in this review of the indications for corneal transplantation that many of the published data on this subject rest not on fact but on opinion. For example, it is difficult to accept the classification of any eye as "very favorable" for corneal transplantation. The description of an eye as "partially favorable" or "less favorable" for keratoplasty is also confusing; one cannot determine whether these terms connote suitability or unsuitability. In the case of uncommon corneal lesions, such as primary fatty degeneration, it is unlikely that any surgeon has performed enough operations to make his results significant. Probably the most important lesson learned in this study is the need for restraint in opinions concerning the indications for this operation. In view of the relatively small number of corneal transplantations yet performed and the multiplicity of diagnoses for the eyes operated on, one must agree that much of the present information is dogmatic, rather than factual.

SECONDARY CORNEAL TRANSPLANTS

A review of the preoperative findings in the cases of secondary corneal transplantations in this series furnishes additional evidence in support of the schema for prognosis suggested here. The result of 1 operation (case 133) was excluded from analysis because of unfavorable preoperative pathologic conditions, but this omission makes no significant change in the visual results for this group (table 1). The preoperative findings for the remaining 34 secondary transplantations are shown in table 7. A detailed comparison of the influence of the various factors in this group is difficult because the visual results were so uniformly unsatisfactory. Visual acuity was either decreased or not significantly changed after operations in 32 cases. The improvement in vision in the 2 cases (152 and 159) in which vision was recorded as "improved" is even open to question, since both patients required strong minus lenses to secure better than 20/200 visual acuity and neither patient is wearing the correction. A review of these secondary operations, then, becomes principally a study of the effect of unfavorable factors in kerotoplasty.

Corneal opacification and vascularization in the eyes undergoing secondary transplantation were generally much more extensive than the conditions in the eyes having a primary operation. Corneal scarring was extensive in 27 cases; the entire cornea was opacified in 15 eyes, and more than one-half the cornea was opacified in 12 eyes. Of the 2 eyes for which the results were considered successful, there was no

corneal opacity in 1 and opacification of more than one-half the cornea in the other. Considerable vascularization of the cornea was present in 25 eyes of this group; this vascularity was described as moderate in 11 and extensive in 14 eyes. Of the 2 eyes for which vision was said to be "improved," there was no corneal vascularization in 1, and no record of vascularity in the other. The visual results in this group of secondary transplantations, then, appear to offer additional evidence that extensive opacification and/or vascularization of the cornea is unfavorable for optical keratoplasty.

Preoperative complications were common in eyes undergoing secondary transplantations. Glaucoma was present before operation in 14 eyes; only eyes with a definite record of increased intraocular tension at the time of operation were included in this number. Anterior synechiae were present in 8 eyes. Cataractous changes were diagnosed in 1 eye. Bulging of a primary corneal graft was described in 3 eyes, and staphyloma of the cornea, in 2 other eyes. It is probable that bulging of previous corneal grafts was more frequent in this group than this figure indicates. Regardless of that possibility, the recorded complications were sufficient to make this group highly unfavorable for corneal transplantation.

A considerable number of preliminary operations were performed on the eyes undergoing secondary transplantation. (In addition, of course, all 34 eyes had previously had a primary corneal graft.) Eleven preliminary operations were performed for the purpose of improving the general condition of the eyeball; these comprised 8 preliminary iridectomies and 3 iridectomies with freeing of anterior synechiae. Nine operations were performed to improve the condition of the cornea; these included superficial keratectomy, corneal curettage, electrocoagulation of blood vessels and excision of corneal staphyloma. Seven operations were performed for increased intraocular tension; they consisted of 2 modified Lagrange operations, 1 trephination, 3 cyclodialyses and 1 cyclodiathermy. In none of these eyes undergoing preliminary operations was a successful result achieved after corneal grafting.

There was no apparent correlation between age, sex, race or the outcome of secondary transplantation. A preoperative prognosis was not found in any of the clinical records of the cases in this group. There was also no apparent relation of the visual results of secondary corneal transplantation to the type of operation, size of the graft, identity of the surgeon or date of the operation.

Comment.—The most obvious lession to be learned from this review of secondary corneal transplantations is that a second transplantation is seldom in order. The visual results in this group were so uniformly poor that the various degrees of opacification and vascularization could

TABLE 7.—*Preoperative and Operative Factors*

No.	Size of Opacity	Vascularization	Preoperative Complications Operations	Age	Sex	Race	Prognosis	Type of Operation *	Size of Graft, Mm.	Visual Result (Final Vision)
131	Entire	Extensive	Secondary glaucoma; anterior synechiae Bulging of the cornea; corneal transplantation	41	M	W	.....	Square	...	Loss of all vision
132	Entire	Extensive	Two preliminary iridectomies; corneal transplantation	39	M	W	.....	Square	...	Unchanged
134	Entire	Extensive	Corneal transplantation	24	M	W	.....	Square	4.5	Unchanged
135	Entire	Extensive	Anterior polar cataract Preliminary iridectomy; corneal transplantation	21	M	W	.....	Square	...	Loss of all vision
136	Entire	Extensive	Corneal transplantation	22	M	W	.....	Square	4.5	Unchanged
137	.....	.....	Secondary glaucoma Two corneal transplantations	24	M	W	.....	Square	...	Unchanged
138	Entire	Moderate	Corneal transplantation; superficial keratectomy	56	F	W	.....	Square	4	Loss of vision
139	Under ⅛	Moderate	Secondary glaucoma Corneal transplantation; complete iridectomy; cyclodialysis with iridectomy; trephining	27	M	W	.....	Square	...	Loss of all vision
140	.....	.....	Secondary glaucoma Corneal transplantation; 2 corneal transplantations with cyclodialysis	24	M	W	.....	Circular	...	Loss of all vision
141	.....	.....	Secondary glaucoma; anterior synechia Corneal transplantation; cyclodiathermy; freeing of synechia	30	M	W	.....	Square	4.5	Loss of vision
142	Over ⅛	Moderate	Secondary glaucoma; anterior synechia Preliminary iridectomy, cyclodialysis; excision of corneal staphyloma; corneal transplantation	28	M	W	.....	Square	4.5	Unchanged
143	Over ⅛	Extensive	Secondary glaucoma Complete iridectomy; cyclodialysis with iridectomy; corneal transplantation	20	F	W	.....	Square	4.5	Unchanged
144	Over ⅛	.....	Secondary glaucoma; staphyloma of cornea Corneal transplantation	27	F	W	.....	Square	4.5	Loss of all vision
145	Entire	Extensive	Multiple peritomy; corneal transplantation	31	M	W	.....	Total superficial	Entire cornea	Unchanged
146	Entire	Extensive	Corneal transplantation; two electrocoagulations of corneal blood vessels	25	M	W	.....	Total superficial	Entire cornea	Unchanged
147	Entire	Extensive	Corneal transplantation; electrocoagulation of corneal blood vessels	27	M	W	.....	Total superficial	Entire cornea	Unchanged
148	Entire	Extensive	Multiple peritomy; corneal transplantation; electrocoagulation of corneal blood vessels; corneal transplantation	31	M	W	.....	Square penetrating	...	Loss of all vision
149	Over ⅛	Moderate	Corneal transplantation	38	F	W	.....	Square	4.5	Unchanged
150	Over ⅛	Moderate	Curettage of cornea; corneal transplantation Anterior synechia	56	M	W	.....	Square	...	Unchanged
151	Entire	.....	Corneal transplantation Anterior synechia; secondary glaucoma	44	M	W	.....	Square	4	Loss of vision
152	Over ⅛	.....	Corneal transplantation	13	M	N	.....	Square	6.5	Improved
153	Under ⅛	Moderate	Corneal transplantation	6	M	W	.....	Square	...	Unchanged
154	Entire	Moderate	Corneal transplantation Anterior synechia; secondary glaucoma Freeing of synechia; preliminary iridectomy	30	M	W	.....	Square	6	Unchanged
155	Over ⅛	Moderate	Superficial keratectomy; corneal transplantation; preliminary iridectomy	42	M	W	.....	Square	5.5	Unchanged
156	Entire	Moderate	Corneal transplantation preliminary iridectomy	28	M	W	.....	Square	6	Unchanged

in Secondary Corneal Transplantations

No.	Size of Opacity	Vascularization	Preoperative Complications Operations	Age	Sex	Race	Prognosis	Type of Operation *	Size of Graft, Mm.	Visual Result (Final Vision)
157	Entire	Moderate	Corneal transplantation Secondary glaucoma modified Lagrange operation	27	M	W	.....	Square	5.5	Unchanged
158	Under ½	None	Corneal transplantation Bulging of cornea; secondary glaucoma Modified Lagrange operation	31	M	W	.....	Square	5.5	Unchanged
159	None	None	Corneal transplantation Bulging of cornea	35	M	W	.....	Square	6.5	Improved
160	Entire	Moderate	Corneal transplantation	36	F	W	.....	Square	5.5	Unchanged
161	Over ½	.....	Corneal transplantation	26	M	N	.....	Square	6	Loss of all vision
162	Over ½	Extensive	Corneal transplantation	30	M	W	.....	Square	6.5	Loss of all vision
163	Over ½	Extensive	Corneal transplantation Anterior synechia; secondary glaucoma Iridectomy and freeing of synechias	52	F	W	.....	Circular	6.5	Unchanged
164	Over ½	Extensive	Corneal transplantation	17	F	N	.....	Circular	6.5	Unchanged
165	Over ½	Extensive	Corneal transplantation Anterior synechia; secondary glaucoma	28	M	W	.....	Square	7.5	Unchanged

* Grafts were of the penetrating type except in 3 cases (145, 146, 147)

not be analyzed separately, as in the preceding discussion of primary transplantations. However, the same conditions that led to a poor prognosis in primary transplantation were increasingly prevalent in these eyes, namely, (1) extensive corneal opacification, (2) extensive corneal vascularization and (3) the presence of preoperative complications. The poor results in this group as a whole tend to corroborate the assumption that keratoplasty will not be successful when the graft remains nearly surrounded by scar tissue after operation. It appears particularly significant that glaucoma was present in 14 of these eyes before operation and anterior synechiae in 8 eyes. This series of secondary grafts also demonstrates the difficulty encountered in attempts to improve the condition of the cornea prior to keratoplasty; the majority of preliminary operations performed on these eyes were unsuccessful.

SUMMARY

1. A survey of the literature concerning the indications for corneal transplantation revealed the following facts:

Conditions generally considered favorable for this operation are (1) interstitial keratitis, (2) keratoconus, (3) hereditary degenerations of the cornea, (4) small corneal opacities with little or no vascularization and (5) large superficial corneal opacities with little or no vascularization.

Conditions generally considered unfavorable for keratoplasty are (1) aphakia, (2) glaucoma, (3) corneal staphyloma, (4) Fuchs's epithelial dystrophy, (5) wide anterior synechiae, (6) extensive

leukomas with heavy vascularization and (7) total leukomas with no normal corneal tissue.

There is no unanimity of opinion regarding the suitability for keratoplasty of the following conditions: (1) corneal fistula, (2) descemetocele, (3) blood staining of the cornea, (4) band-shaped keratitis, (5) primary fatty degeneration of the cornea, (6) corneal burns due to tear gas, (7) scars showing calcareous degeneration, (8) the corneal lesions of pemphigus, (9) lime burns of the cornea and (10) posterior synechias.

There is no agreement concerning the contraindications for corneal transplantation. Almost all the unfavorable conditions listed here are considered contraindications by one or more surgeons.

The terms employed by some authors in discussions of prognosis in this operation are confusing. The use of the designation "very favorable" is not warranted by the results of this procedure. The terms "less favorable" and "partially favorable" are also confusing; one cannot determine whether they mean favorable or unfavorable.

The purpose for which the operation was performed is not clear in some reports. The visual results of optical transplantation cannot very well be compared with the results of cosmetic, tectonic, prophylactic or therapeutic transplantation.

A common finding is the expression of an opinion concerning prognosis based on experience with a small number of operations on one of the uncommon corneal diseases; such opinions obviously have no statistical significance.

2. Nine operations in this series of 165 corneal transplantations were excluded from this review of indications because of pathologic conditions existing prior to operation that obviated improvement in visual acuity. Amblyopia ex anopsia was present in 6 cases; lesions of the central fundus existed in 2 cases, and multiple pathologic conditions in 1 case. The remaining 156 operations were divided into two groups: (1) the 122 primary corneal transplantations, and (2) the 34 secondary corneal transplantations, the latter being separated because of the peculiarities of the lesions in the eyes undergoing secondary grafting.

3. A survey of the preoperative findings in the 122 primary corneal transplantations of this series is summarized as follows:

Judged on the basis of diagnosis, visual results were best in keratoconus and poorest in chemical burns of the cornea. The results in eyes with interstitial keratitis were not significantly better than the average results for the series; this observation is not at all in accord with the reported results of the operation in this disease.

It appears significant that none of the operations performed on eyes with a degenerative process of the cornea were successful.

The visual results improved in inverse proportion to the size of the corneal opacity. The results in this series further suggested that the actual size of the leukoma may not be important so long as there is enough normal corneal tissue surrounding the graft after operation.

The visual result also improved in inverse proportion to the amount of corneal vascularization. However, results were as good in eyes with little corneal vascularity as the results in eyes with no corneal blood vessels.

None of the eyes with anterior synechiae or glaucoma achieved improvement in visual acuity after operation.

Preliminary operations exerted little or no beneficial influence on the results in this series.

Age and sex showed no significant correlation with the results.

Visual results were better in Negroes than in white patients, but the number of operations on Negroes was too small to give this finding any significance.

No correlation between the recorded preoperative prognosis and the postoperative visual result could be determined.

4. A survey of the factors pertaining to the operative procedure, i. e., type of operation, size of graft, identity of surgeon and year of operation, disclosed no relation of any of these factors to the results of the operation.

5. The results in this series of primary corneal transplantations indicate that there is no strict correlation between the diagnosis of the corneal lesion and the visual result of the operation. On the other hand, there appears to be a definite relation of some pathologic characteristics of the lesion to the final visual result. On the basis of the findings in this series, a simplified schema for prognosis in corneal transplantation is offered.

6. The conventional terms "favorable," "unfavorable" and "operation contraindicated" appear adequate for description of the prognosis in this operation.

7. A review of the preoperative findings in the secondary corneal transplantations of this series disclosed the following:

Visual results again improved in inverse proportion to the extent of corneal opacification and/or vascularization.

Preoperative complications were common in this group of cases of secondary transplantations. Glaucoma and anterior synechiae were most frequent. None of these eyes with additional complications achieved a successful result.

Preliminary operations were performed before many of the secondary transplantations; these included operations to improve the eyeball

generally, to improve the condition of the cornea and to lower the intraocular tension. None of these operations were followed by a successful keratoplasty.

No correlation was found between the operative result and the age, sex or race of the patient. Likewise, no correlation was seen between the final result and the type of operation, the size of the graft, the identity of the surgeon or the date of operation.

8. Lack of pertinent data precludes an opinion on the indications for cosmetic, tectonic, prophylactic and therapeutic corneal transplantation.

704 State Tower Building.

HIGH SPEED PHOTOGRAPHY OF THE ANTERIOR OCULAR SEGMENT

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BROOKLYN

HIGH speed photography affords the use of a new technic in photographing the external eye. The essential feature of the unit consists of an electrical flash tube developed by Edgerton.[1] The illumination afforded is extremely brilliant (about 42,000,000 lumens) and of very short duration (0.001 second) and produces no discomfort to the patient. From a single tube 10,000 or more light flashes can be obtained. There is no appreciable sense of heat to the patient, even when the light is placed as close as 4 inches (10 cm.) from the eye. The after-image produced is inconsequential.

A slender glass tube measuring about 3 inches (7.5 cm.) in height and filled with xenon gas is used. When the electric charge is released from a power pack, ionization of the gas results and a brilliant flash is produced. The quality of the light is uniform and substantially correct for daylight color film. The power pack employed is similar to that used in radio or television. It operates on a 110 volt alternating house current stepped up to 2,500 volts and stored in special condensers. The charge is released by a trigger gun when one is ready to flash the electric tube.

In photography of the external eye special problems are encountered.

1. The lid reflexes, presenting one of the chief problems, are *(a)* the normal blinking reflex, which lasts about one-third second and occurs on an average of every five minutes; *(b)* the sensory blinking reflex, better known as the corneal reflex, which has an average duration of one-tenth second, and *(c)* the optical blinking reflex, which has an average duration of one-fifth second.

2. The eyes are never completely at rest, owing to the inherent tonus of the extraocular muscles. Fine twittering excursions and coarser rotary movements of the eyeball can be appreciated with high power slit lamp microscopy.

Presented at a meeting of the New York Academy of Medicine, Section of Ophthalmology, Jan. 17, 1949.

1. Edgerton, H. E.: Photographic Use of Electrical Discharge Flashtubes, J. Optical Soc. Am. **36**:390-399 (July) 1946.

3. Because of the convexity of the cornea and sclera, it is difficult to obtain sufficient depth of field to record a large section of the eye in clear focus on a flat film.

4. The eye is a sensitive organ and has a limited tolerance to prolonged strong illumination. This condition becomes exaggerated when the eye is diseased and in high-strung persons and children.

5. The cornea behaves as a convex mirror, and when light is directed on it, a corneal reflection of the illuminating source is obtained. At

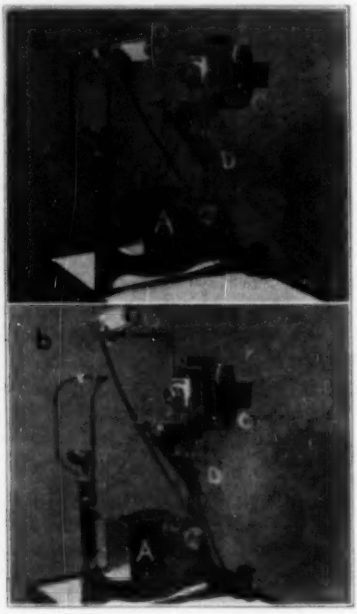

Fig. 1.—Photographic unit. In *a*, *A* indicates power pack; *B'*, electrical flash tube on right-angled metal rod; *C*, 2¼ by 3¼ inch speed-graphic® camera, and *D*, focusing light.

In *b*, *B* indicates electrical flash tube on right-angled rod raised to produce deviation of corneal reflex.

times the pathologic condition which is being photographed is obscured by the size and position of the corneal reflex.

6. The normal eye is recessed in the orbit so that the eyebrow and overhanging orbital edge may produce annoying shadows. The cilia of the upper lid may also throw their shadow on the cornea, masking important details.

PHOTOGRAPHIC APPARATUS

In order to overcome most of these difficulties, a photographic unit was assembled which consisted mainly of a speed-graphic® camera with attached electric flash tube, and both mounted on a sturdy metal stand. The usual chin and head rest used for slit lamp examination was incorporated in the unit. Color film, 2¼ by 3¼ inches (ektachrome,® kodachrome® and ansco®) or black and white film was used. By means of special opaque cut-out occluders, placed in proper position in the film holder, four 35 mm. exposures could be obtained on one 2¼ by 3¼ inch negative. Critical focusing on details to be photographed was accomplished by the ground glass of the camera.

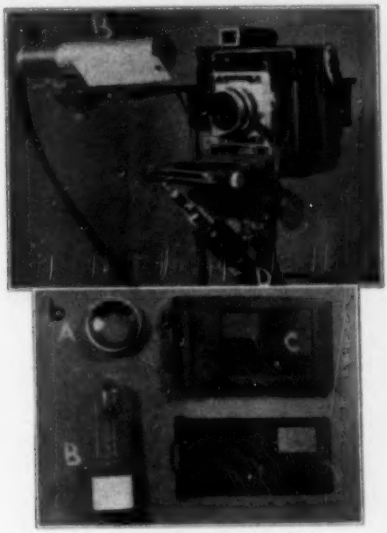

Fig. 2.—(*a*) Close-up of photographic unit. *B* is electrical flash tube enclosed within reflector, with plastic shield covering front of tube, and *D*, focusing rheostat light.

In *b*, *A* is portrait lens; *B*, electrical flash tube, and *C*, film holder with cut-out occluder for 35 mm. pictures.

The camera was set on a rack and pinion, and it was easy to obtain forward, backward and lateral movement. By this means screw motions of the rack and pinion permitted additional fine focusing. Life-sized (1 : 1) or greater photographic magnification was obtained by double bellows extension and the use of supplementary plus lenses (1 to 5 D.).

The camera shutter was synchronized with the source of illumination and was set at 1/100 second. The time setting is unimportant because of the extremely short duration of the flash. For color film, the diaphragm was usually set at f. 8, and for black and white work an opening of f. 32 to f. 100 could be used with a very fast film, such as Eastman Tri X Pan.®

A small focusing light, composed of a rheostat in a Bausch & Lomb handle and an ordinary small, 2.6 volt tungsten bulb, was attached by means of a metal collar around the tubular base of the photographic unit. It could be swiveled and bent in position when directed at the eye to be photographed.

The flash tube and gun were mounted on a sturdy right-angled metal rod, which was attached to the right side of the camera. By means of a special screw device, the light source was easily moved to a distance of 4 inches from the eye. A small white plastic shield was securely placed in front of the tube to diffuse the corneal reflection and to protect the eye against possible tube breakage. A silvered metal reflector around the tube concentrated the source of the light and afforded additional protection. By elevation of the rod at a desired distance, the position of

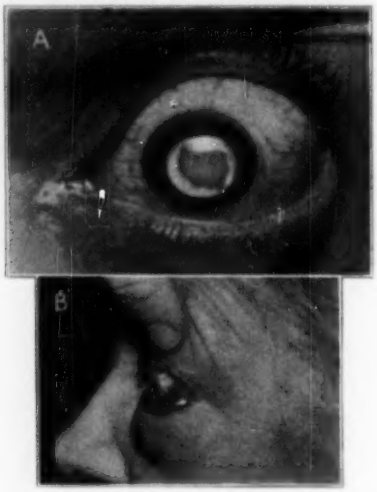

Fig. 3.—Photographs taken with unit. *A*, subluxated complicated cataract; *B*, proptosis in a case of arteriovenous aneurysm.

the corneal reflex could be shifted upward, so that important corneal details were not obscured.

SUMMARY AND CONCLUSION

I have used high speed photography for the past two years with excellent results and no appreciable annoyance to the patient. The technic has been standardized so that the operation of the photographic unit becomes almost automatic. The power pack which is used to flash the tube can be of a portable type or may be attached to the usual house current. Any type of camera in which the shutter is preferably synchronized with the light source is satisfactory. This method of photography eliminates the problem of ocular motion and minimizes

the corneal reflex. It can also be adapted to use in other branches of medicine. The light source is well balanced for color photography, and the same flash tube can be used repeatedly, thereby lowering the cost of operation.

Because of the extreme depth of focus that can be obtained with small lens apertures in the use of black and white film, excellent enlargements can be made up to a magnification of 35. Enlarged photographic reproductions of the limbal capillaries and aqueous veins, heretofore impossible to photograph, have been obtained.[2] Similarly, the cornea, iris and visible portion of the lens are also available for study. This new technic, therefore, opens new avenues of photographic investigation in ophthalmology.

160 Henry Street.

2. Gartner, S.: Blood Vessels of the Conjunctiva: Studies with High-Speed Macrophotography, Arch. Ophth. **32**:464-476 (Dec.) 1944.

Clinical Notes

A NEW SCLEROTOMY KNIFE

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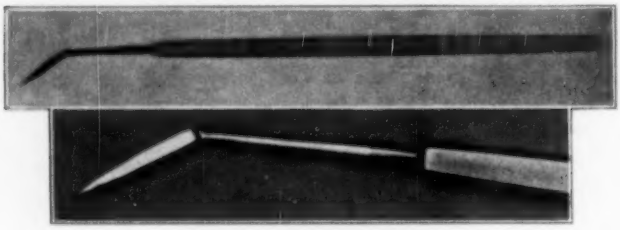
NEW YORK

A SCLEROTOMY knife is here presented.[1] The need for this knife is based on the fact that the scleral incision for iridectomy ab externo, iridencleisis, cyclodialysis, scleral resection or incision for removal of a foreign body through the posterior route is a delicate and careful procedure. If the incision is done too rapidly and too deeply, the uveal tract may be incised and vitreous may prolapse.



Sclerotomy knife.

The blade itself forms an obtuse angle of approximately 135 degrees with the handle. The widest portion near the handle is 1.25 mm.; it then narrows to a sharp point. The entire blade is about 1.2 cm. in length. The lower surface is sharp and bevels upward. The upper surface has a cutting edge which extends from the point for a distance of 3 mm.

This knife has the following advantages: 1. Because of its angle, it facilitates the incision and makes it easier to use the lower (belly) cutting edge. 2. As soon as most of the sclera has been cut, the front of the knife can be used as a pick, and the incision can be enlarged by use of the upper cutting surface. 3. This method of incision prevents the knife from going too deep and cutting the uveal tract.

1. This knife is available through E. B. Meyrowitz Surgical Instruments Co., Inc., New York 18.

A LIGHTING SYSTEM FOR PHOTOGRAPHY OF THE EYE

ROBERT R. CHACE, M.D.
and
JAMES H. LAFAYETTE
NEW YORK

TWO PROBLEMS face the photographer of the eye who wishes to take external pictures in color. The first is to obtain sufficient light; the second is to avoid the unpleasant effect of too much light on the patient's face. It has been our experience that the intensity of light together with the heat given off by incandescent sources causes a great deal of discomfort to the patient. The majority of persons have considerable sensitivity to both light and heat. When to this is added the ocular irritability already present from disease, one has a poor condition for photography of the eye.

At the Institute of Ophthalmology, our department of photography has for years used as a light source 500 watt projection lamps. These are mounted in a housing with a focusing lens. This source was used both for focusing the camera and for making the exposure. The heat caused drying of the cornea. Later, a series-parallel switch with resistor was installed to reduce the amount of light during focusing, but this still did not remove the discomfort while the exposure was being made.

Accordingly, we turned to the stroboscopic light for a source of illumination. Several considerations led us to this decision. The light had to have the proper intensity. It had to be of the proper color temperature. As little heat as possible should be given off. Finally, the period that the light was on should be as short as possible. The stroboscopic light is a specially constructed gas tube that gives off a short, powerful flash after an electric charge is built up. This can be repeated as current is built up in condensers. Little heat is given off, and the speed with which the flash comes causes little annoyance to the patient. We have found the Wilcox portable strobo-lite* to be very satisfactory. The portable type of light is best for our needs because it is mobile.

Figure 1 shows the lamp mounted on a stand, the former being attached to a transverse metal clamp by means of a universal joint. To a transverse metal rod below is fastened a General Electric 75 watt photospot* light for focusing. On the table stands the power pack containing the electronic equipment together with two storage batteries. In front of the power pack is shown a standard battery handle with control switch to fire the light. The interval between flashes required for build-up is about nine seconds, and the light may be fired more than two hundred times before the battery needs to be recharged. This may be done overnight in the usual manner.

Figure 2 shows the light system in position with the camera and at a distance of 45 cm. from the patient's face. We use a Leica model G

From the Department of Photography, Institute of Ophthalmology of the Presbyterian Hospital of New York City.

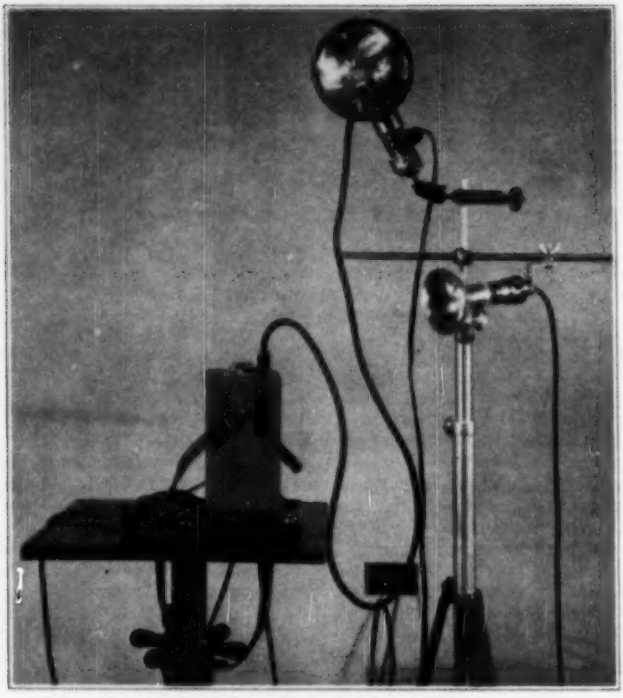


Fig. 1.—Lighting system in detail.

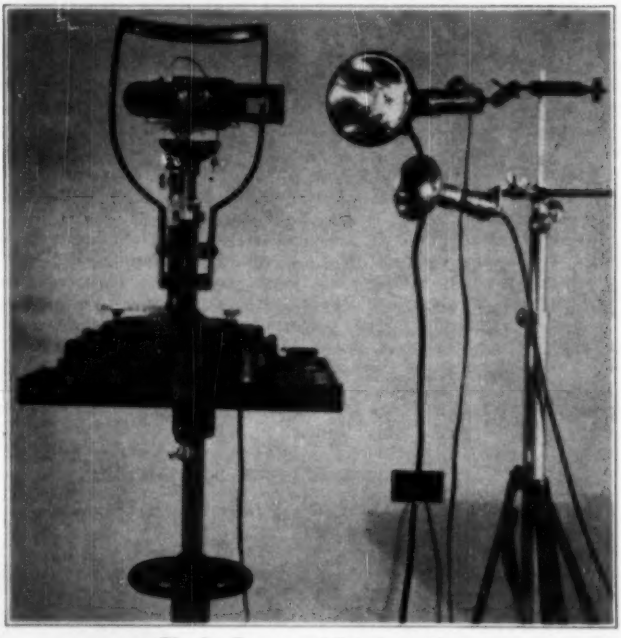


Fig. 2.—Camera and light in position.

with an Elmar 5 cm. 1:3.5 lens and a 6 cm. tube. Focusing is done with a sliding attachment. Exposure is made with an open shutter with the diaphragm set between 6.3 and 9. At present we are using the Eastman CC 24 filter, the light having a color temperature of 7,000 ° K. The film used is Eastman Daylight K 135. The color quality of the pictures is most satisfactory, and we feel that this system has eliminated many of our difficulties. It is especially useful in photographing the eyes of children because of its speed.

635 West One Hundred and Sixty-Fifth Street.

AN OPHTHALMOSCOPE FOR USE IN OPERATIONS

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JOHANNESBURG, SOUTH AFRICA

IT IS generally recognized that ophthalmoscopic control is a *sine qua non* for the surgical repair of retinal detachment. Both the direct and the indirect technics as usually practiced have well known disadvantages in the theater—loss of time with either method, danger of sepsis with the former.

The apparatus to be described was first devised for the removal of a cysticercus from the vitreous.[1] Its application to the surgical treatment of other conditions followed automatically.

A head lamp for use in operations, like that commonly used by otolaryngologists, was fitted with a perforated mirror so that it was possible to look through the hole in the mirror along the axis of the reflected beam of light, as with an ophthalmoscope (fig. 1). It was subsequently found that a similar suitable apparatus is available commercially.[2] A pair of + 4.0 D. sph. spectacles is worn. The upper and lower segments of each lens have been removed, leaving a central rectangular portion, the whole resembling an ordinary operating loupe (fig. 2). A prismatic element is not incorporated, although some operators might find this an added advantage. If a distance correction is normally worn, the + 4.00 sphere can be incorporated into a bifocal lens, the addition being made as a small, almost central, segment. With the head lamp donned, the mirror is adjusted over one eye (dominant) and the beam focused to an area about ¾ inch (1.9 cm.) in diameter at a distance of about 10 inches (25 cm.). All screws are now firmly tightened. The cord is disconnected from the source of current, and the surgeon scrubs up.

With the use of both eyes a good view of the operative field is obtained. With the "mirror eye" a red reflex can be seen in the patient's pupil, and on approaching a little one obtains a good view of the periphery of the fundus. In persons with moderate hypermetropia the depth of the fundus is visible as well. With the aid of minus lenses held

1. Epstein, E.: Intra-Ocular Cysticercosis: Report of a Case, South African M. J. **22**:625 (Oct. 9) 1948.

2. The "National" mirror reflecting head light.

and manipulated like the condensing lens in the indirect method of ophthalmoscopy, but kept close to the eye examined, the disk and the macular area can be seen in near emmetropic and myopic eyes.

By means of a + 20.00 D. condensing lens, the fundus can be examined by the indirect method of ophthalmoscopy. With the direct method, therefore, both hands are usually free; with the indirect method, one hand is free.

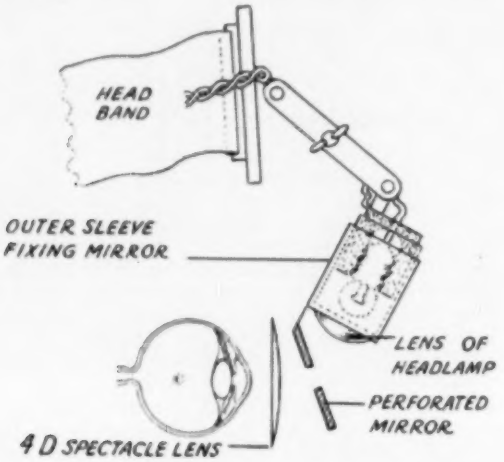

Fig. 1.—Sketch of the ophthalmoscope for use in operation (Epstein[1]).

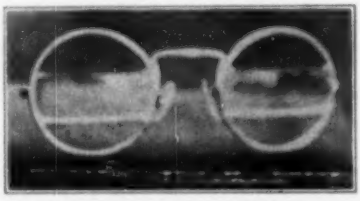

Fig. 2.—Photograph of the spectacles to be worn.

In many cases it is possible to apply a suitable electrode and, by dimpling the sclera, watch and thereby localize its position with reference to the fundus. With the diathermy current switched on, it is possible to watch the effect develop in the retina and to stop when desired. This technic has been found invaluable in the few cases of macular hole with detachment which has been so treated during the past year. A single 1 mm., right-angled needle electrode (Safer or Kronfeld) is applied as near the macula as possible under direct vision. (The external rectus muscle is first divided, and an Arruga speculum, pref-

erably of nonconducting material, held by the assistant, is used to maintain an open tunnel.) The shank of the needle is curved to conform to the shape of the globe.

The small side lights usually present in theaters can be left burning all the time. There is no need of the periodic total black-out required with the usual technics. As the surgeon is wearing the ophthalmoscope constantly, no time is lost in preparing for ophthalmoscopic examination.

As already mentioned, the apparatus was first used for the removal of a cysticercus from the vitreous under visual control. The condensing lens was held in one hand; a specially prepared pair of forceps, with extra long, thin shanks, was held in the other, and its passage through the vitreous to grasp the parasite was watched and guided constantly. The operative field was prepared as follows:

Retrobulbar injections of procaine hydrochloride with epinephrine was given to anesthetize and soften the globe; surface diathermy was employed, and a trapdoor scleral flap was formed, with sutures for closing first inserted before the incision was carried through the choroid and retina. Only a minimum of vitreous—the amount adherent to the forceps—was lost. One and a half years after operation the eye was still in excellent condition; no vitreous bands were apparent, and danger of detachment seemed definitely excluded.

Similarly, a nonmagnetic intraocular foreign body has been removed from the vitreous, and nine months later, at the time of this report, the eye was still in excellent condition, with vision of 6/5.

The apparatus has also been found useful for sketching the fundus, one hand being left free for holding the pencil.

409 Medical Centre, Jeppe Street.

Correspondence

OPERATION FOR PTOSIS

To the Editor.—The recent paper "Operation for Ptosis Utilizing the Superior Rectus Muscle," by Dr. R. N. Berke, which appeared in the December issue of the ARCHIVES, brings to mind an anatomic relationship of importance in the performance of many operations of the Motais type, and one which, to the best of my information, has not previously been mentioned.

The correction of ptosis in these operations, according to Shoemaker (*Ann. Ophth.* 1907), in an opinion concurred in by Spaeth, is brought about by establishing an adhesion between the lid and a fixed position on the globe. This position in many of the modifications of the Motais operation, such as Berke's ingenious operation and the Dickey fascia lata sling procedure, is established at or near the insertion of the superior rectus.

If, for example, the lid were anchored by adhesion between the upper border of the tarsus and the insertion of the superior rectus, the lid margin after operation would be at a point below the level of the insertion, corresponding to the width of the tarsus at its widest. Duke-Elder gives the distance of the insertion from the corneal limbus as 7.75 mm. and the average width of the tarsus as 10 to 12 mm. It is obvious, then, that in the example stated the final level of the lid margin would on the average be 2 to 4 mm. below the corneal limbus. However, these figures are average ones in the adult, and it is a matter of common observation that even in the adult they may vary widely, particularly with regard to the width of the tarsus. The insertion of the superior rectus may also vary with the refractive condition of the eye.

The insertion of the superior rectus is not always taken as the fixed point in these procedures; indeed, it is rarely so taken. The conditions of each individual modification of the Motais operation are such that the anchorage varies in location with respect both to the upper tarsal border and to the insertion of the superior rectus. For example, in Berke's operation the elevation of the upper margin of the tarsus cannot exceed the level of the insertion of the superior rectus, but it may be less. In the Dickey operation it may be more or less, depending on the fact that the sling is placed at a point above the insertion and is attached to the tarsus at a variable tension.

This variable factor, the point of adhesion of the lid to the globe, may be altered in the operative procedure as dictated by the degree of preoperative ptosis. However, to achieve greater accuracy, it is suggested that the other variable quantities, that is, (1) the distance of the insertion of the superior rectus from the corneal limbus and (2) the width of the tarsus, be measured at the time of operation. A comparison of the two measurements will decide whether the point of adhesion should be between the upper margin of the tarsus and the insertion of the superior rectus or at some other point which would produce either more or less elevation, as desired.

This is not to say that it is possible in this way completely to obviate the inherent inaccuracies of muscle surgery. It is believed, however, that a certain number of overcorrections and undercorrections can be avoided.

VICTOR GOODSIDE, M.D., New York.

1777 Grand Concourse (56).

CORNEAL TRANSPLANTATION

To the Editor.—In the article "Corneal Transplantation: Visual and Cosmetic Results," which appeared in the December 1949 ARCHIVES, page 813, Dr. Fredrick C. Stansbury has singled out for caustic comment the article on corneal transplantation which appeared in the October 1947 issue of *Hygeia* under my name. "Publicity of this type," he writes, "has misled the public into believing that corneal transplants are a cure for total blindness and that new eyes can be transplanted to replace diseased ones." This is a matter of serious concern to me, since the article in question was written at the request of the editor of *Hygeia* for the express purpose of presenting to the layman, in simple language, the facts about corneal transplantation. It stated quite clearly the conditions under which a transplantation of cornea might be indicated, and it placed emphasis on the fact that the cornea alone was transplanted.

Surely Dr. Stansbury underestimates the intelligence of the readers of *Hygeia*, who apparently read the article in its entirety and were not misled by a sentence or two taken out of context. It may be reassuring to know that since the publication of the article I have not received a single inquiry about "transplantation of eyes to replace diseased ones." In fact, the article, to my knowledge, has not evoked a single communication of any kind, direct or indirect, from a person who thought he might be aided by a corneal transplantation.

Dr. Stansbury's thoroughly tabulated analysis of the cases of keratoplasty on the basis of visual improvement and the breakdown into etiologic groups is subject to the same criticisms which he directs at the statistics presented at the symposium of the American Academy of Ophthalmology and Otolaryngology and at other statistics. The truth is that, with the exception of the most favorable cases, such as those of keratoconus, every case considered for keratoplasty is in a category of its own. Such important factors as selectivity of cases, the state of preservation of the donor cornea and the skill and experience of the surgeon do not lend themselves to tabulation. It is implied in the author's reevaluation of cases previously included in the symposium of the American Academy that since the percentage of successful cases is smaller the conclusions must be more valid. Following this line of reasoning, those conclusions would be most valid whose author has had no successful cases at all!

MAX FINE, M.D., San Francisco.

655 Sutter Street (2).

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

USE OF PLACENTAL EXTRACT IN TREATMENT OF HERPETIC KERATITIS AND SUPERFICIAL PUNCTATE KERATITIS. B. KRONENBERG, Am. J. Ophth. **31**: 1101 (Sept.) 1948.

Kronenberg describes the preparation of aqueous placental extract and reports favorably on its use in treatment of herpetic and superficial punctate keratitis. They could not corroborate Filatov's favorable results with its use in cases of retinitis pigmentosa.

W. S. REESE.

INTERSTITIAL KERATITIS OCCURRING IN A CASE OF REITER'S DISEASE. E. E. CASS, Brit. J. Ophth. **33**: 454 (July) 1949.

Cass reports a case of Reiter's disease in which the ocular symptoms consisted of interstitial keratitis combined with keratitis profunda.

W. ZENTMAYER.

TREATMENT OF HERPES CORNEAE, SUPERFICIAL PUNCTATE AND EPIDEMIC KERATITIS WITH BEE VENOM. V. MUCH, Ophthalmologica **115**: 89 (Feb.) 1948.

A preparation of bee venom (apicur®) was given intracutanously in increasing amounts. The author points out that the value of bee venom in treatment of rheumatoid diseases of the eye has been known for many years, and he finds that patients with the nonrheumatoid conditions mentioned in the title benefit remarkably from this treatment.

H. P. KIRBER.

TREATMENT OF SERPIGINOUS ULCER. A. STEIN, Ophthalmologica **117**: 227 (April-May) 1949.

The author designed a plastic cup with an elastic rim that can be adapted to the orbital margin. The cup is held in place by means of a rubber band. Ten cubic centimeters of a solution of penicillin (20,000 units per cubic centimeter) fills the cup, and it is kept in contact with the cornea for six hours. The treatment is combined with penicillin iontophoresis. The therapy was required for ten days on the average, and the causative organisms were staphylococci, pneumococci and diplococci.

H. P. KIRBER.

Experimental Pathology

AN EVALUATION OF AN ANTIHISTAMINIC DRUG IN EXPERIMENTAL UVEITIS. I. H. LEOPOLD, W. DEAN and H. BLAZAR, Am. J. Ophth. **32**: 31 (Jan.) 1949.

Leopold, Dean and Blazar found that tripelennamine (pyribenzamine®) hydrochloride prevented the development of an anaphylactic

type of uveal inflammation when given prior to the toxifying injection of horse serum but failed when given with this injection.

W. S. Reese.

General Diseases

Ocular Manifestations of Pemphigus Foliaceus. F. Amendola, Am. J. Ophth. 32: 35 (Jan.) 1949.

Amendola reviews the literature on pemphigus foliaceus and enumerates its ocular manifestations, particularly cataract. He speculates on the possibility of researches into the latter, which might throw light on the genesis of cataract.

W. S. Reese.

Anthrax of the Eye. H. D. Barnshaw and J. C. Lovett, Am. J. Ophth. 32: 106 (Jan.) 1949.

Barnshaw and Lovett review the types, incidence and ocular manifestations of anthrax and report a case of rapidly progressive edema of the eye. Recovery with cicatricial ectropion occurred. This defect was corrected by means of a full thickness graft from the upper lid of the fellow eye.

W. S. Reese.

Ocular Findings in One Hundred and Twenty-Eight Juvenile Diabetics. I. Givner and C. Lodyjensky, New York State J. Med. 47:1371 (June 15) 1947.

In routine fundoscopic examination of 128 diabetic children, Givner and Lodyjensky found 3 who had retinal hemorrhages and 1 diabetic cataract. Since none of the patients had complaints referable to vision, and since the importance of retinal hemorrhages in a better evaluation of the case has been emphasized, it would seem good practice to study every diabetic patient under mydriasis. Special emphasis should be put on pinpoint hemorrhages and aneurysmal capillary dilatations, as they can be easily overlooked.

J. A. M. A. (W. Zentmayer).

Sjögren's Disease, with Dryness of the Bronchial Mucosa and Uncertain Lung Lesion. P. Ellman and F. P. Weber, Brit. M. J. 1: 304 (Feb. 19) 1949.

After a description of keraconjunctivitis sicca (Sjögren's disease), in which the ocular symptoms play so important a part, the authors report a case in which they found a new symptom, namely, dryness of the bronchial mucosa; the other symptoms in this case were dryness of the mouth and conjunctiva and mild rheumatoid arthritis. The authors regard the disease as a lymphoid granulomatous condition affecting principally the salivary and lacrimal glands. The various points in differential diagnosis are discussed. Treatment consists in inhalation therapy, closure of the lacrimal ducts by diathermy and high voltage roentgen therapy.

Arnold Knapp.

TOXIC PAPILLORETINITIS COMPLICATING PULMONARY TUBERCULOSIS. L. GAT, Ophthalmologica **117:** 43 (Jan.) 1949.

Gat examined the fundi of 200 patients in a sanatorium and found typical changes in 10 per cent. He observed an initial edema of the optic nervehead, manifested by a blurred margin, mainly the nasal, upper and lower portions. The adjacent retina also showed mild edema. In the next stage, the edema subsided, the nasal margin became more distinct and perivascular formation of connective tissue was noticed. In the final stage, the disk appeared normal, there was no edema of the retina and large connective tissue bands surrounded the veins. The article is illustrated with drawings of the fundus and photographs of histologic sections.

H. P. KIRBER.

CAUSES OF DEATH IN OPHTHALMOLOGIC PRACTICE. A. JOKL, Ophthalmologica **117:** 129 (March) 1949.

A systematic survey of the causes of death in ophthalmologic practice has been compiled for the first time. The author made a thorough search of the literature and has written an interesting paper, but one which does not lend itself to abstracting. The incidence of death from ocular causes is about 1 per million inhabitants. The long list starts with hemorrhage in hemophilia and includes septicemia and meningitis following conjunctivitis; there were 10 cases of death following hordeolum and rare cases of death due to plague following infection of the conjunctiva with infected sputum, perforating injuries followed by gas gangrene, parasitic infection and malignant tumors of the eye. Fatal traffic accidents of drivers with contracted fields and such accidents as are indirectly due to the wearing of bifocal lenses should be kept in mind, though they are not being reported in the literature. Ways and means to prevent death in ophthalmologic practice are briefly discussed.

H. P. KIRBER.

Glaucoma

PIGMENTARY GLAUCOMA. H. S. SUGAR and F. A. BARBOUR, Am. J. Ophth. **32:** 90 (Jan.) 1949.

Sugar and Barbour present 2 cases of glaucoma of a type designated as pigmentary glaucoma, which they believe to be a distinct entity.

W. S. REESE.

TREATMENT OF GLAUCOMA WITH CYCLODIATHERMY. W. G. MARR, Am. J. Ophth. **32:** 241 (Feb.) 1949.

Marr concludes that theoretically, since cyclodiathermy produces atrophy of the ciliary body, it should decrease the formation of aqueous. The operation, therefore, should be beneficial in those eyes in which the normal filtration mechanism has been occluded and in which supplementary filtration cannot be established. Clinical experience, however, would indicate that the chronic glaucoma which is intractable to miotics and the usual surgical procedures rarely can be controlled by either the nonperforating or the partial penetrating type of cyclodiathermy that has been employed.

W. S. REESE.

SOME OBSERVATIONS ON MIOTICS. E. B. DUNPHY, Am. J. Ophth. 32: 399 (March) 1949.

Dunphy concludes that in spite of an enormous amount of work done on the subject it is still not known just how miotics lower the tension. Clinical experience and experimental work suggest a combination of miosis and a breakdown in the blood-aqueous barrier with changes in the osmotic relation.

Some drugs produce more vasodilation and cyclotonia than others, although their miotic effects may seem to be the same. These vasodilating and cyclotonic actions of miotics are probably of considerable importance in determining their effect on the intraocular pressure.

Instillation of 1 per cent phenylephrine hydrochloride combined with a miotic should be a rational procedure in treatment of glaucomatous eyes with shallow angles, especially when the miotic has strong vasodilating and cyclotonic actions.

Although ophthalmologists are learning more and more about the iris angle through gonioscopy, they are still not in a position to predict just what type of glaucoma will respond to miotics.

In general, miotics are valuable in early cases of both acute congestive and chronic simple glaucoma in bringing the tension under control while the patient is being evaluated for proper surgical procedure. They are also extremely helpful after operations which just miss being entirely successful. Although miotics alone may carry a few patients with glaucoma along satisfactorily for years, they must be considered an adjunct to, rather than a substitute for, surgical treatment.

W. S. REESE.

NASAL CONTRACTION OF VISUAL FIELDS IN GLAUCOMA. W. ARKIN, Am. J. Ophth. 32: 407 (March) 1949.

Arkin notes that the cause of nasal contraction of the visual field in glaucoma has never been satisfactorily explained. The best known theory is the blood circulation theory.

He submits as additional considerations the oblique course of the optic nerve, which makes the length of the fibers greater at the temporal part of the retina, and the consequent difference in the pressure acting on the opposite sides of the physiologic or pathologic excavation, as well as the difference in tissue resistance on the nasal and the temporal margin of the disk.

W. S. REESE.

MODE OF ACTION OF NONPERFORATING CYCLODIATHERMY. L. WEEKERS, R. WEEKERS and F. ROUSSEL, Ophthalmologica 117: 65 (Feb.) 1949.

Following their method described in 1946, the authors apply an electrode of 0.75 mm. diameter for fifteen seconds 7 mm. behind the limbus. The temperature should not exceed 90 C. Twelve to twenty applications of the electrode are recommended. After the operation the pupil does not react to cocaine but responds promptly to acetylbetamethylcholine and to epinephrine. These changes are due to the dis-

turbance of the sympathetic and parasympathetic nerves, which are injured in their course in the suprachoroid. Nonperforating cyclodiathermy also destroys the vasomotor nerves of the uvea and causes vasodilatation of the uveal vessels. This, in turn, has some influence on the water metabolism of the eye, leading to a permanent decrease in the intraocular pressure.

H. P. KIRBER.

INTRAVENOUS USE OF PROCAINE IN TREATMENT OF GLAUCOMA. I. ESENTE, Ophthalmologica **117**: 147 (March) 1949.

A slow intravenous injection (five to ten minutes) of a 2 per cent solution of procaine hydrochloride (10 to 20 cc.) was found to be of benefit in treatment of acute congestive glaucoma. The patient's general condition improves rapidly, and the intraocular pressure begins to decrease about two hours after the injection and reaches its lowest reading about six hours later. Eight cases are presented, and the mode of action of procaine on the water balance of the eye is discussed.

H. P. KIRBER.

Methods of Examination

VISUAL DIAGNOSIS OF EYE DISEASES BY MEANS OF INFRA-RED RADIATION. A. VAŠKO and M. PELEŠKA, Brit. J. Ophth. **31**: 419 (July) 1947.

Experiments were made with image converters which were sensitive to infra-red radiation in an attempt to aid in the diagnosis of certain diseases of the eye. The image converter transforms the infra-red image of the observed eye on the cathode into a visible image on a fluorescent screen. Observation in infra-red light proved to be especially useful as a supplement to the conventional methods of ophthalmologic diagnosis before transplantation of the cornea and similar present day, frequently performed operations. The article is illustrated.

W. ZENTMAYER.

A POINT FOR CONSIDERATION IN THE USE OF THE STEREOSCOPE. F. W. LAW, Brit. J. Ophth. **32**: 639 (Sept.) 1948.

Law considers the problem of what happens to the inclination of the visual axes on moving the stereogram in a stereoscope toward or away from the observer. It is found that the interocular distance is a factor of fundamental importance. When the card is placed at the focal plane of the stereoscope lenses, convergence is independent of interocular distance. The same stereogram moved in the same direction and through the same distance induces an increase of convergence when the interocular distance is 5.2 cm., a smaller increase when it is 5.4 cm. and an actual decrease when it is 5.8 cm. With the card at 25 cm., a greater interocular distance involves a reduced degree of convergence. Once one has decided for what exact purpose one requires a patient to use a stereoscope, it is essential to choose an appropriate instrument and, having measured the patient's interocular distance, to calculate how the instrument will have to be used and to instruct the patient

accordingly. Tables have been constructed showing the actual deviation of the visual axes involved for varying widths of the stereogram and varying positions of the picture. W. ZENTMAYER.

DOUBLE STAINING FOR BULK SPECIMENS OF RETINA AND CHOROID. A. LOWENSTEIN, Brit. J. Ophth. **32:** 748 (Oct.) 1948.

The author describes the technic recommended, which is simple and does not presume histologic experience. Even a busy practitioner may learn to do the work unsupported by a technician. The following summary is given: Double staining with hematoxylin and scarlet red, with clearing of the tissue, is recommended for bulk specimens of retina and choroid. The method offers a better chance of discovering such vascular anomalies as pathologic anastomoses, aneurysms, subendothelial necrosis and exudates in the retina, especially if fat plays a part. It allows a careful study of the choriocapillaris and sometimes reveals fatty changes in isolated choroidal vessels. The branched chromatophores in the outer choroidal layers are frequently filled with fat, in cases of uveitis, and they are considered to be phagocytic reticulum cells. W. ZENTMAYER.

Neurology

ARACHNOIDITIS OPTICOCHIASMATICA: REPORT OF A CASE. W. VOGELSANGER, Ophthalmologica **114:** 273 (Oct.-Nov.) 1947.

A soldier who was admitted to the hospital for "snow blindness," had poor vision and greatly contracted fields, with a normal appearance of both fundi. In a few weeks both disks became pale, but vision and the fields improved. Soon thereafter central scotomas appeared, with headache and fever. Surgical exploration showed thick bands of arachnoid tissue in the cisterna chiasmatis. These were freed with electrocoagulation, and the fields and vision improved, despite pale disks, to 6/6 in one eye and to 6/60 in the other. H. P. KIRBER.

PARESIS OF OCULAR MOVEMENTS. F. RINTELEN, Ophthalmologica **114:** 325 (Oct.-Nov.) 1947.

A case of paresis after cerebral concussion showed tonic spasm of convergence, spasm of accommodation, pupillotonic reactions, disturbance of conjugate movements and horizontal jerky nystagmus. The author places the lesion in the subthalamic region. H. P. KIRBER.

OCULAR MANIFESTATIONS OF MYASTHENIA GRAVIS. M. APPELMANS and H. VAN VOOREN, Ophthalmologica **117:** 8 (Jan.) 1949.

A case of infantile myasthenia gravis is described in which the pseudoparalytic symptoms of the mimic muscles, and of the coordinated ocular movements predominated. These symptoms appeared to be due to hypertony of the cholinergic system on the basis of a dysfunction of the endocrine organs, particularly the thymus. The close resemblance of the symptoms of myasthenia and those of botulism is pointed out. Neostigmine and roentgen irradiation of the thymus are recommended as treatment. The pharmacodynamic action of neostigmine, DFP (di-isopropyl fluorophosphate), acetylcholine and curare as related to myasthenia gravis is discussed in detail. H. P. KIRBER.

GLIOMA AND PSEUDOGLIOMA OF THE OPTIC CHIASM. L. PAUFIQUE and R. ETIENNE, Ophthalmologica **117:** 90 (Feb.) 1949.

Three cases are described in great detail. In the first a glioma of the optic chiasm involved the intraorbital portion of the optic nerve; in the second typical symptoms of a chiasmal tumor were presented but the condition proved to be an unusual form of neuropticoencephalitis; in the third, one of a typical glioma, the ocular signs developed with extreme slowness.

H. P. KIRBER.

Ocular Muscles

THE VERTICAL ELEMENT IN THE CAUSATION OF SO-CALLED HORIZONTAL CONCOMITANT STRABISMUS. E. B. SPAETH, Am. J. Ophth. **31:** 1553 (Dec.) 1948.

Spaeth emphasizes the relation of so-called concomitant squint to disturbances in the vertically acting muscles. He stresses single binocular vision rather than cosmetic improvement as the aim of surgical intervention.

W. S. REESE.

MYOKYMIA OF THE EYELIDS. I. GIVNER and N. S. JAFFE, Am. J. Ophth. **32:** 51 (Jan.) 1949.

Givner and Jaffe state that in 15 cases of myokymia of the eyelids the condition was treated successfully by the oral use of quinine, and that the possibility of similar control of muscular twitchings after use of physostigmine and di-iso-fluorophosphate (DFP) is now being investigated.

W. S. REESE.

A NEW CLASSIFICATION OF NONPARALYTIC STRABISMUS. S. V. ABRAHAM, Am. J. Ophth. **32:** 93 (Jan.) 1949.

Abraham presents a simple classification of nonparalytic strabismus in which he attempts to correlate the basic physiologic principles involved with the types of strabismus found.

W. S. REESE.

SYNKINETIC OVERACTION OF THE INFERIOR OBLIQUE MUSCLE. G. P. GUIBOR, Am. J. Ophth. **32:** 221 (Feb.) 1949.

Guibor concludes that synkinetic overaction of the inferior oblique muscle is of common occurrence. It probably results from radiation of impulses. Nonsurgical treatment should be tried before myectomy or recession of the inferior oblique muscle is resorted to.

W. S. REESE.

USE OF MIOTICS IN TREATMENT OF CONVERGENT STRABISMUS AND ANISOMETROPIA. S. V. ABRAHAM, Am. J. Ophth. **32:** 233 (Feb.) 1949.

Abraham concludes that there can be little doubt that miotics, if properly used, may become a valuable addition to our armamentarium in the treatment of strabismus, especially after equalization of vision.

The response to miotics in some cases of amblyopia suggests an unsuspected lack of accommodation. Here the miotic may act as a tonic to stimulate the ciliary muscle.

The use of miotics may give one the opportunity to delay or avoid the use of glasses in cases of hypermetropia with or without strabismus or anisometropia. The miotic may permit the replacement of the central accommodative activity fully or partially for distance and for near vision. The action of the miotic is entirely peripheral.

The thoughts expressed here, together with the preliminary presentation of data, indicate the desirability for further research.

W. S. Reese.

Vertical Nystagmus on Direct Forward Gaze with Vertical Oscillopsia. M. D. Bender and W. F. Gorman, Am. J. Ophth. **32:** 967 (July) 1949.

Bender and Gorman report 2 cases of vertical nystagmus on direct gaze. Both patients complained of images bobbing up and down—vertical oscillopsia. When the nystagmus ultimately subsided, the oscillopsia disappeared. Intravenous injection of sodium amytal® (amobarbital sodium) or alcohol temporarily abolished the vertical nystagmus and the concomitant vertical oscillopsia. Differentiation is made between the acquired and the congenital type of vertical nystagmus on direct forward gaze.

W. S. Reese.

Role of the Platysma Muscle in Torticollis Deformity. A. D. La Ferte, Plast. & Reconstruct. Surg. **2:** 72, 1947.

The author states that if the head is turned, as in wryneck, the eyes cannot look straight ahead, with the visual axes parallel, without extreme tension on the ocular muscles. Diplopia is therefore produced. This cannot be borne with comfort. It becomes the habit in such circumstances for one eye to suppress. These observations differ from the results of some other investigators who have made a clinical study of ocular torticollis.

L. P. Guy.

Pleioptic and Orthoptic Treatment. A. Stein and A. Bangerter, Arch. d'opht. **8:** 156 (Feb.) 1948.

This article is a description of methods used in a school for pleioptic and orthoptic treatment in the ophthalmologic clinic of De Saint-Gall. This school is made up of two classes, the one for monocular exercises and the other for binocular education. In the treatment of amblyopia, it is not the duration of occlusion which is important, but the intensity of work during the occlusion. The children attend the school for an hour two or three times a week. The first half-hour is devoted to monocular training by various methods. The second half-hour is used for appropriate monocular and binocular play. The children are encouraged to practice these exercises at home. The article presents photographs of several types of apparatus used in these procedures.

S. B. Marlow.

DIPLOPIA WITH CONVERGENT SQUINT IN MYOPIC ADULTS (BIELSCHOWSKY). E. WEBER, Ophthalmologica **114:** 320 (Oct.-Nov.) 1947.

In 1922 Bielschowsky described a rare disturbance of oculomuscular coordination in myopic adults. There is gradual onset of diplopia for distance. The findings usually are esophoria for distance with a constant angle of squint which is the same in primary and in secondary deviation. To be excluded in differential diagnosis are spasms of accommodation, paralysis of divergence and incorrectly centered glasses. The author reports 2 cases and notes that the bulbi converge to a point 50 cm. to 1 meter distant. When tests were carried out with double prisms, an excessive breadth of fusion was noted—33 to 34 degrees. Bielschowsky advised advancement of the external rectus muscles, but the author finds that vision in his cases is well improved with adequate prisms base out for distance.

H. P. KIRBER.

Operations

USE OF RAT TAIL TENDON FOR CORNEAL SUTURES. A. GARDILCIC, Ophthalmologica **117:** 115 (Feb.) 1949.

In 1929 Pischl recommended the use of the tendon of the rat tail for corneal sutures in cataract extraction. Gardilcic experimented on rabbit and human eyes with corneal sutures made of several substances: silk, hair of a Japanese woman, kangaroo tendon, human fascia lata, tendon of the extensor hallucis and tendons from the tails of the horse, ox, pig, cat and rat. He recommends the tendon of the rat tail for the following reasons: It is easily available; it can be prepared by the surgeon himself; it is well tolerated by the human eye, and it becomes absorbed in about seven days. The technic of preparing this suture material is described in detail.

H. P. KIRBER.

Orbit, Eyeball and Accessory Sinuses Parasites

CHRONIC ORBITAL MYOSITIS AND IMPORTANCE OF VENOUS LESIONS IN THE ORBIT. J. BABEL, Ophthalmologica **114:** 312 (Oct.-Nov.) 1947.

The characteristic symptoms of chronic orbital myositis are as follows: exophthalmos without deviation, nonreducible, intermittent but progressive; absence of pain; insidious onset; limitations of movements of the eyes, and passive immobility of the globes. This type of myositis is observed exclusively in the orbit and is bilateral in 25 per cent of cases. All the other muscles are normal; the blood count is normal; the pituitary and thyroid glands are normal. A case is reported in which the orbit was explored. Biopsy of muscle showed that mingled among normal fibers were fibrous tissue and inflammatory infiltrates, atrophic fibers and beginning hyalinization. All degrees of muscular dystrophy are to be seen, such as vacuolation and granular degeneration. Arteries show occasional endothelial proliferation and are surrounded by lymphocytic infiltrates. Veins show lymphocytic infiltration

and plasma cells in the adventitia, with occasional accumulations of these cells in the media. The infiltrates do not form follicles; they show no reticular arrangement or germinative center, such as appear in inflammatory pseudotumors of the orbit. The disease is therefore an inflammatory process of unknown origin involving the fat, the muscles and the vessels of the orbit. H. P. KIRBER.

FAMILIAL OCCURRENCE OF PULSATING EXOPHTHALMOS. K. LISCH, Ophthalmologica **117:** 180 (March) 1949.

In a man aged 23 spontaneous pulsating exophthalmos developed. During the exploration of the right orbit a soft bleeding mass was encountered, and exenteration of the orbit became necessary. The sister of the patient was seen at the age of 45 because of the same disease. The left eye was 7 mm. more prominent than the right and presented all the signs of pulsating exophthalmos. The left internal carotid artery was ligated. Two years after the operation the patient presented identical symptoms in her right eye. She died of apoplexy a few days after admission. The father of these 2 patients had died of apoplexy at the age of 47. He had had pulsating exophthalmos of the right eye for two years. According to the authors, this case is the first recorded instance of a familial occurrence of this disease. H. P. KIRBER.

Physiology

QUALITATIVE EXAMINATION OF MACULAR FUNCTION. M. AMSLER, Ophthalmologica **114:** 248 (Oct.-Nov.) 1947.

The author describes a new type of screen consisting of white lines on a black background which form squares of 5 mm., as viewed from a distance of 28 to 30 cm., or an angle of 1 degree. The total screen measures 10 cm. and appears at an angle of 20 degrees at a distance of 30 cm. The advantage of such a screen for the testing of macular function is explained at length. The method was found of use particularly in cases of circulatory disturbances of the paracentral area of the retina and in cases of recent chorioretinitis. H. P. KIRBER.

PERCEPTION OF MOTION IN LIGHT AND DARK ADAPTATION. M. HODEL-BOOS, Ophthalmologica **115:** 25 (Jan.) 1948.

Experiments were conducted on light and dark adaptation, using a kymographion with variable speeds of rotation and illumination. The increase in the thresholds of light and dark adaptation showed a ratio of about 1:3 to 1:4. The author was prompted to conduct these investigations by the frequent occurrence of accidents among passengers alighting from cars during the black-out. H. P. KIRBER.

Refraction and Accommodation

PRACTICAL PROBLEMS PERTAINING TO PRESBYOPIA. J. E. LEBENSOHN, Am. J. Ophth. **32:** 22 (Jan.) 1949.

Lebensohn reviews tests for presbyopia and discusses the choice of bifocal spectacles, anisometropia, horizontal prismatic effects, subnormal vision and trifocal spectacles. W. S. REESE.

REFRACTIVE TREATMENT OF ASTHENOPIA. P. W. MILES, Am. J. Ophth. **32:** 111 (Jan.) 1949.

Miles submits a practical procedure for handling difficult problems of refraction, incorporating cyclodamia and binocular technic. Various practical tests are discussed. He attempts to keep the writing on a student level. W. S. REESE.

ACCOMMODATIVE DEFECT FOLLOWING ATMOSPHERIC CONCUSSION. H. E. SMITH, Am. J. Ophth. **32:** 959 (July) 1949.

Smith reports 4 cases of atmospheric concussion, with examinations at post-traumatic intervals varying from ten days to twelve months. In all these cases neuropsychiatric consultations were provided. Smith concludes that atmospheric concussion may produce an ocular syndrome characterized by deficiency of accommodation, retinal edema, mild choroiditis and constriction of peripheral fields. W. S. REESE.

Retina and Optic Nerve

END RESULTS IN RETINAL DETACHMENT. L. J. CROLL and M. CROLL, Am. J. Ophth. **31:** 1107 (Sept.) 1948.

The authors discuss retinal detachment and report their findings in 15 cases, in all of which operation was performed.

W. S. REESE.

SENILE MACULAR LESIONS. R. I. LLOYD, Am. J. Ophth. **31:** 1135 (Sept.) 1948.

Lloyd gives an interesting review of senile lesions of the macula and concludes that a number are actually stages of a degenerative process affecting mainly the lamina basalis (Bruch), the vessels of the choriocapillaris and the pigment layer. He emphasizes the importance of the use of the binocular ophthalmoscope. W. S. REESE.

ANGIOMATOSIS RETINAE WITH REPORT OF PATHOLOGICAL EXAMINATION. H. NEAME, Brit. J. Ophth. **32:** 677 (Sept.) 1948.

Neame reports a case of angiomatosis in a woman aged 28. Both eyes were treated by electrolysis. Vision before institution of treatment was 6/5 part in the right eye and 6/60 in the left eye. The left eye was treated with electrolysis. Twelve years later vision was 6/18 part in the right eye and was limited to perception of light with faulty light projection in the left eye.

A pathologic study was made of an eye in which a diagnosis of angiomatosis had been made seven years previously. The vitreous cavity was almost entirely obliterated by complete retinal detachment. A few small round cells and fibroblasts were near the reflection of the retina at the ora serrata. In the posterior folded part of the detached retina were blood vessels of large caliber with a number of smaller vessels lying among retinal elements, the layers of which could not here

be identified. Partly surrounding several of the large vessels were masses of red blood cells, hemorrhages which may have been responsible for the recent subacute glaucoma. There was no trace of any wall or boundary to indicate localization of the vascular growth. In fact, an abundance of vessels extended in the section for almost twice the extent of the growth, about 6 mm. in all. The subretinal space was partly occupied by granular exudate containing numerous migrated rounded pigment cells with circular nuclei. The choroidal vessels were full of red blood cells, and a fairly widespread round cell infiltration involved the spaces between the vessels.

W. ZENTMAYER.

ANGIOID STREAKS OF THE RETINA AS A TRANSITORY PHENOMENON. C. PASCHEFF, Arch. d'opht. **8:** 152 (Feb.) 1948.

The author reviews briefly the literature on this condition and describes the typical appearance of angioid streaks of the retina. It is only within recent years that it has been noted that these streaks may appear and disappear, and he cites the case reported by Zentmayer (ARCH. OPHTH. **35:** 541 [May] 1946). From May 1940 until late in 1946, the author had under observation a patient aged 32 in whom he saw the angioid streaks disappear. From observations on both eyes of this patient, he concludes that two kinds of branching occur—the red and the silver gray. He states that the streaks are often complicated by hemorrhages in the macular region, which may clear without any damage to the visual acuity. While the pathogenesis is not known, he believes that there is a metabolic disturbance which involves the pigment and suggests that there may be some relation to the cholesterol in content of the blood.

S. B. MARLOW.

PRIMARY PIGMENTARY DEGENERATION OF THE RETINA IN SYMMETRIC SECTORS. F. VERREY, Ophthalmologica **114:** 278 (Oct.-Nov.) 1947.

The common finding in cases of advanced primary pigmentary degeneration of the retina is contraction of the visual fields with some extension to the temporal side. An unusual case is described in which the main defects were in the upper field in both eyes and in the temporal inferior quadrant in the right eye. The fundi showed corresponding deposits of pigment. The arteries in the nonaffected retina were normal; those in the affected retina were strikingly constricted.

H. P. KIRBER.

Sympathetic Ophthalmia

PROBLEM OF SYMPATHETIC OPHTHALMIA. B. SAMUELS, Am. J. Ophth. **31:**397 (April) 1948.

Samuels, in this Montgomery Lecture delivered in Dublin, discusses sympathetic ophthalmia from the clinical, pathologic, etiologic, prognostic and therapeutic aspects in a comprehensive and interesting manner.

W. S. REESE.

FLUORESCEIN TEST FOR SYMPATHETIC OPHTHALMIA. M. AMSLER and A. HUBER, Ophthalmologica **117:** 202 (April-May) 1949.

The permeability of the ciliary body to fluorescein is much increased after trauma, particularly so after perforating injuries. The healthy fel-

low eye shows a normal fluorescein permeability curve. The authors collected 56 cases of perforating injuries, performed the permeability tests and found 11 cases in which the healthy eye showed increased permeability. Since fluorescein permeability is also increased in cases of iridocyclitis, it was assumed that the test is of value in early diagnosis of sympathetic ophthalmia, before any other clinical signs appear.

H. P. KIRBER.

Therapeutics

EXPERIENCE WITH PLACENTAL IMPLANTS. M. NEUENSCHWANDER, Ophthalmologica **117**: 290 (April-May) 1949.

Fifty-seven patients with pigmentary degeneration of the retina were treated with subconjunctival injections of placental serum. Of these patients, 6 were selected for follow-up because of improvement in their condition. One year after termination of the treatment the conditions of the 6 patients were as follows:

Patient 1: Vision not improved; visual field improved; dark adaptation worse.

Patient 2: Vision not improved; fields originally improved, now in the pretreatment state; changes in dark adaptation same as those in fields.

Patient 3: Vision originally improved, now unchanged owing to complicated cataracts; visual fields improved; dark adaptation worse.

Patient 4: Vision same; fields improved; dark adaptation worse.

Patient 5: Vision remained slightly improved; fields improved; dark adaptation worse.

Patient 6: Vision and fields remained improved; dark adaptation unchanged.

Since no other means are known for the treatment of retinitis pigmentosa it is suggested that placental implants or serum be used. Some patients will show improvement, primarily with respect to the visual fields.

H. P. KIRBER.

Tumors

ANGIOSARCOMA OF THE ORBIT. P. V. CARELLI and J. P. CANGELOSI, Am. J. Ophth. **31**: 453 (April 1) 1948.

Carelli and Cangelosi report a case of angiosarcoma of the orbit in a 11 year old girl. The tumor was removed, and there was no metastasis at the end of thirty months.

W. S. REESE.

DIATHERMY TREATMENT OF ANGIOMA OF THE RETINA. P. M. LEWIS, Am. J. Ophth. **31**: 829 (July) 1948.

Lewis reports 2 cases of angiomatosis treated with diathermy coagulation. He believes that surface diathermy with multiple punctures into and around the angioma is the method of choice.

W. S. REESE.

DIAGNOSIS OF ORBITAL TUMORS BY ANGIOGRAPHY. A. GRINO and E. BILLET, Am. J. Ophth. **32**: 897 (July) 1949.

Grino and Billet present 2 cases of orbital tumor and 1 of intracranial tumor, in all 3 of which the history and symptoms were similar.

Accurate localization was made possible by angiographic studies. The technic of cerebral angiography is outlined, and the authors recommend its use in preference to more dangerous and less informative methods.

W. S. Reese.

Amputation Neuroma in the Orbit. F. C. Blodi, Am. J. Ophth. 32: 929 (July) 1949.

Blodi reviews the literature on amputation neuromas in the orbit and reports a case following an enucleation for retinoblastoma.

W. S. Reese.

Primary Malignant Melanoma of the Optic Disk. F. Cordes and M. J. Hogan, Am. J. Ophth. 32: 1037 (Aug.) 1949.

Cordes and Hogan present a case of primary malignant melanoma of the optic disk in a Negro woman aged 52. The growth appeared to arise from the tissues of the optic nerve anterior to the lamina cribrosa.

W. S. Reese.

Vision

Visual Protection in Aerial Warfare. P. C. Livingston, Brit. J. Ophth. 32: 689 (Sept.) 1948.

Livingston supplies a summary and draws the following conclusions: The preservation of sight can be aided by the use of bullet-proof glass screens and armor plates fitted within the structure of the aircraft. Further protection can be effected by equipping air crews with flying goggles or spectacles fitted with safety glass windows, which can be ground so as to provide correction in cases of refractive error, or by fitting contact lenses in certain cases in which the refractive error cannot otherwise be adequately treated. The eyes behind contact lenses can move over a wide range without loss of acuity. Visual training offers a valuable indirect method of protection through instruction of personnel in careful scanning procedure, in how to make the best use of rod vision under states of low illumination and quickening the powers of recognition of the objects detected. The records of ocular injury sustained by personnel of the Royal Air Force in flying operations lend weight to the belief that a planned campaign against the hazard of loss of sight reaps its rewards.

W. Zentmayer.

So-Called Color Stereoscopy. J. W. Waagenaar, Ophthalmologica 117: 74 (Feb.) 1949.

Figures or letters on a colored background are frequently used by commercial artists for the stereoscopic effect they produce. The author discusses the causes of this effect and comes to the conclusion that it is independent of binocular vision and of colors. It is due to the superposition of the image and the after-image in oscillating fixation. Nine illustrations are included.

H. P. Kirber.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

W. Guernsey Fray, M.D., Chairman

Maynard C. Wheeler, M.D., Secretary

Regular Meeting, Jan. 19, 1948

INSTRUCTION HOUR

Gonioscopy. DR. PETER C. KRONFELD, Chicago (by invitation).

CASE REPORT

Heredodegeneration of the Macula: Occurrence in a Family Group. DR. FRANK R. BUSSEY (by invitation) and CAPTAIN W. L. BERKLEY (MC), U. S. N. (by invitation).

A family tree showing definite occurrence of macular degeneration in 8 cases and possible occurrence in 3 other cases was presented. Certain common associated disorders were noted in many of these cases; these include similar ophthalmoscopic appearance, hypermetropia with or without astigmatism, muscular imbalances, central scotoma, temporal pallor of the nerve head and (though not previously mentioned in the report) red hair and color blindness. The onset of symptoms seemed related to periods of physiologic stress, and the cases could be grouped as occurring in infancy, puberty, adolescence, early childhood and the presenile period. The hereditary transmission in this family was that of a "dominant trait with imperfect penetrance."

DISCUSSION

DR. RALPH I. LLOYD: There seem to be four types of hereditary macular degeneration. The first type is characterized by large white spots but excellent vision until later in life. This type has appeared in the literature as Doyné's familial honeycomb choroiditis. It is surprising how advanced the changes may be with but little effect on vision.

The second type is much rarer and is characterized by fine white dots, either discrete, as in Lauber's fundus albipunctatus cum hemeralopia, or literally sprinkled all over the fundus, with ring scotoma, night blindness and, eventually, blindness. The Lauber type may be a milder form of the severe type, which is described under the title "retinitis punctata albescens." No tissue from the second type has been studied microscopically, so far as I know, and only 1 case of the much commoner first type has been so studied, and that by Treacher Collins.

The third type, known as juvenile maculocerebral degeneration, is best understood because it is possible to obtain tissue for examination from institutions or hospitals. If the disease appears before puberty,

cerebral degeneration occurs, and this is characterized by degeneration of the ganglion cells of the retina, optic thalamus and cerebellum. Patients whose disease appears after puberty may, and usually do, lose their sight but may not have the cerebral complication.

The fourth type, to which the present cases belong, is characterized by an atrophic process of the macular area of the choroid and retina with more or less disturbance and accumulation of pigment. No tissue from this type has ever been examined in the laboratory. Cases of unilateral involvement have been described in the literature, but those described here are the first to be well established. It is possible that the younger of the 2 patients with unilateral macular degeneration may later show the same changes in the second eye, but in the case of the older patient enough time has passed without the development of this added difficulty to make one reasonably sure that it will not occur

Another aspect of recording and watching the progress of this disease is the expense involved. The cost of making colored drawings has increased, and I have been compelled to discontinue the practice. The patients cannot pay the expense of a photograph or a painting, and photography is not as easy or as successful as painting. I should like to compliment the authors on their excellent presentation, and I hope that they will come back in five and ten years to tell us what happens in these cases.

PAPERS OF THE EVENING

Use of Miotics in Treatment of Convergent Strabismus and Anisometropia: A Preliminary Report. DR. SAMUEL V. ABRAHAM, Los Angeles (by invitation).

Miotics were used in cases of hypermetropia in which, incidentally, there was convergent strabismus with or without anisometropia. The miotics used were pilocarpine hydrochloride, 1 and 2 per cent solutions; physostigmine salicylate, 0.25 per cent, and di-isopropyl fluorophosphate (DFP), 0.1 per cent. These drugs produced miosis and a spasm of accommodation which was measurable and due entirely to peripheral stimulation. Di-isopropyl fluorophosphate had the most prolonged effect, 1 drop sometimes lasting six or seven days. The pilocarpine produced a reaction of shorter duration and required instillation two or three times a day.

There were 44 cases of convergent strabismus of the isometropic type in which the visual acuity was equal, or approximately equal, in the two eyes before the use of miotics. In 22 of these cases the strabismus was periodic in type at the onset and remained so until the miotic was used. In 16 of the cases, the eyes when under the effect of the miotic showed single binocular fixation and no further strabismus, without requiring glasses. In 5 of these cases, after varying periods of the use of miotics, the eyes remained straight even after discontinuation of the miotic. In the second group of 22 cases, the strabismus was constant in type, being either unilateral or alternating when first seen. In 16 of these cases the type of strabismus had been changed by previous treatment to the periodic type before the miotic was used, and visual acuity was equal, or approximately so. In 15 of these 16 cases the use of the miotic kept the eyes straight without glasses or any other treatment. In 3 of these cases the eyes remained straight after discontinuation of the miotic. In 5 of the 6 cases in which the squint was constant

before use of the miotic, the drug was of benefit. In 3 of these cases the eyes remained straight after discontinuation of the miotic. In many of these cases the eyes were straight with glasses, which could be dispensed with by the use of miotics. In none of these cases was orthoptic training given. In 2 cases of strabismus with anisometropia the eye with the highest error of refraction was treated with the miotic, with improvement in 1 case and no effect in the other. In 4 cases of anisometropia without strabismus, the patients were comfortable and preferred using the drops in the ametropic eye rather than wear glasses.

DISCUSSION

Dr. Harold Brown (by invitation): Did any of Dr. Abraham's patients have an increase in their esotropia? In cases of exotropia with hypermetropia, what effect did miotics have on the divergence?

Dr. Ralph I. Lloyd: I should like to ask Dr. Abraham on what theory this treatment operates.

Dr. Joseph Pascal (by invitation): Dr. Abraham said that in 4 cases of anisometropia without strabismus the use of miotics helped the condition. In what way did it help the condition? Was the refractive error equalized by the use of miotics in both eyes, or what?

Dr. David Wexler: Were results obtained in cases of alternating esotropia in which the hypermetropic error was small?

Dr. Samuel V. Abraham, Los Angeles: I appreciate so many questions. My main purpose in coming to New York was to stimulate wide discussion of this treatment, in the hope that it will be tried out in some of the large clinics, where it can be evaluated more quickly. It took me eight years to collect these results from my own practice.

In answer to Dr. Brown: I found no overcorrection of the strabismus in any case. The miotic was not tried in cases of exotropia. There is no doubt that miotics produce miosis. The pupils measure about 1 mm. with di-isopropyl fluorophosphate. If there is very much miosis, the error of refraction is more than corrected by the miotic. The miotic actually produces a spasm of accommodation. One should use a drop of the weakest solution of the miotic that gives the result, and I find 1 or 2 per cent pilocarpine hydrochloride most easily tolerated.

In reply to Dr. Wexler: In a few cases I used miotics when no particular error of refraction was present and still obtained good results in 60 per cent. In most cases the strabismus was alternating before the miotic was used.

In answer to Dr. Pascal's question: The miotic was used in the more highly ametropic eye, and the vision of this eye was thus improved without the use of glasses. The patients were more comfortable and happier than with a pair of glasses. Probably the better equality in image size obtained with miotics was a factor in the patient's greater comfort. There is no doubt that the miotic changes the refraction temporarily

In answer to Dr. Lloyd: The theory behind the treatment is not entirely clear. What I am reporting is the result. I was trying miotics to change the refraction permanently when I noted this particular result. However, for the accommodation-convergence relation (I should like to say that it is a very loose one) this reaction to miotics seem to offer

support. The central stimulation of accommodation is immediately lessened, with a pronounced effect on the convergence. The strabismus disappears almost immediately.

Practical Management of Fatigue of Accommodation. Dr. Hunter H. Romaine (by invitation).

The author discussed a practical approach to the management of the fatigue of accommodation. The diagnosis is made by a careful anaylsis of the accommodation, muscular balance and general findings. The primary problem is correction of the underlying cause which may be a generalized disease or a focal infection. During the period of investigation, stimulation of the accommodation and convergence by exercise is suggested, and when this is impossible the use of clip-on plus spheres and base-in prisms is indicated. These are used only during the period of disability. For patients who cannot be cured work that does not involve extreme ocular activity should be selected.

DISCUSSION

Dr. Willis Knighton: The idea of supplementing the insufficient function of accommodation with lenses and prisms is not new. The device has been tried innumerable times—sometimes successfully, sometimes not.

Two factors are usually held responsible for fatigue of accommodation. One is sclerosis of the lens, making this structure incapable of responding to the usual activity of the ciliary muscle. This factor is a physical one, regardless of its cause, and nothing can be done to change it. The loss of accommodation is fairly definite, within narrow limits, and must be compensated for by lenses.

The second factor is physiologic and has to do with weakness of the ciliary muscle itself. The causes of this weakness are those which bring about fatigue in any muscle—general debility, toxins, overwork and insufficient rest. Unless the underlying cause is found and corrected, as Dr. Romaine has emphasized, exercises and optical corrections are not likely to help. When pure fatigue from overwork is responsible, there is no substitute for rest. But physical and physiologic conditions are not always entirely responsible. A psychogenic factor often plays an important part in the reactions of the patient. It may be born of anxiety or of dislike for the task at hand or of other (subconscious) emotions. It is not easy to recognize, especially for the ophthalmologist, nor is it easy to treat. It may result in spasm of accommodation, producing pseudomyopia, or in relative weakness of accommodation.

I recall a first year medical student whose accommodation seemed to fail just before examination time. He had a moderate amount of hypermetropia, but correction with glasses did not help. Close work blurred after intervals which became increasingly shorter until finally he had to give up reading entirely. At the same time a retinal fatigue developed, and there was contraction of the peripheral fields. No organic cause was found. After his final examinations, which he barely passed, he decided not to continue medicine. A change to cattle raising, on a ranch of his own, gave him a new interest and complete freedom from all ocular symptoms.

A complete approach to the treatment of accommodative fatigue must include a consideration of all possible factors. Without a comprehensive view, no "practical" approach can have rational value. Dr. Romaine has not overlooked the importance of this preliminary study but has chosen to concentrate on the mechanics of treatment. I believe that his principles are practical, in properly selected cases, because they have worked for me.

Dr. Joseph I. Pascal (by invitation): Dr. Romaine's work might be supplemented by the application of an objective test for the determination of weakness of accommodation. With subjective methods alone it is sometimes difficult to tell how weak the accommodation is. But if an objective test is used, the strength and weakness of the accommodative functions can be inferred, checked and corroborated. One way of studying the accommodation objectively is by means of so-called dynamic retinoscopy, in which a study of the behavior of accommodation under stress is made.

The physician can place his target as close to the eye as he wishes, say 2 or 3 inches (5 or 7.5 cm.), and watch the reflex while the patient makes a great effort to accommodate. I suggest this method as an auxiliary means in studying the strength and weakness of the accommodative functions.

Dr. Hunter H. Romaine: I have not done any work of the kind mentioned by Dr. Pascal, but I am glad that he made the suggestion and shall be interested in following it up.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

Edwin B. Dunphy, M.D., President

Merrill J. King, M.D., Secretary-Treasurer

Regular Meeting, Feb. 18, 1948

CASE PRESENTATION

Cases of the following conditions were presented and discussed: (1) blindness and third nerve paralysis due to adenocarcinoma of the ethmoid sinus; (2) bilateral uveitis and tumors of the sclera which histologically were diagnosed as fibromas; (3) recurrent serous retinitis in one eye developing three days after the known onset of a dental abscess; (4) argyrosis of the skin due to ingestion of a silver compound prescribed for the treatment of gastric ulcer; (5) idiopathic fragmentation of the iris.

PRESENTATION OF PAPERS

Glaucoma. Dr. Paul A. Chandler, Boston.

This paper, the third in a series of lectures on glaucoma, was concerned chiefly with buphthalmos and with juvenile and hereditary glaucoma. For buphthalmos, goniotomy performed after the manner of Barkan was recommended, provided the surgeon had had sufficient training in the technic. Failing this, iridencleisis was stated to be the operation of choice. It was pointed out that an essential part of the treatment was massage of the eyes by the parents for an indefinite period after operation.

Juvenile glaucoma was said to present features not commonly seen in the glaucoma of middle and old age. In the early stage there may be an acute rise of tension to a high level, and this condition may respond dramatically to miotics and the tension be controlled for a long period. Unless there is perfect control with use of drops, a filtering operation is recommended in all cases of juvenile glaucoma, especially if any cupping of the disk or loss of field has taken place.

The essayist pointed out the relative rarity of hereditary glaucoma. He suggested that it is due to a hereditary defect which in a given family may bring on glaucoma at approximately the same age in all members of the family. More than one member of a family is often seen with primary glaucoma, but the author suggested that this is due to the anatomic makeup of the eye, and is different from true hereditary glaucoma. Operation was advised in all cases of hereditary glaucoma, since the condition is rarely adequately controlled with medical therapy.

A Hypothesis Concerning Amblyopia ex Anopsia. DR. ELEK J. LUDVIGH, Boston.

The author presented quantitative experimental data showing that in some patients with amblyopia ex anopsia the foveal light difference sensitivity of the amblyopic eye is as good as that of the sound eye when the test object is a disk subtending 25 degrees of arc. However, as the angle subtended by the test object is decreased, the light difference sensitivity of the amblyopic eye becomes poorer than that of its fellow.

The hypothesis is advanced, with supporting evidence, that on-off elements, assumed to exist in the human eye, mediate binocular fixation, contour perception and visual acuity and that these elements, or the neural output thereof, are "suppressed" in the initial stages of amblyopia ex anopsia.

Radioautographic Studies on the Eye. DR. LUDWIG VON SALLMANN, New York.

Radioactive sodium was used to obtain radioautograms of microscopic sections and frozen slices of rabbit eyes. This method was applied to study the penetration from the general circulation into the ocular fluids, resorption from the vitreous and diffusion within the vitreous of living and enucleated rabbit eyes, and to illustrate some of the advantages and limitations of iontophoresis.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Perce DeLong, M.D., Chairman

M. Luther Kauffman, M.D., Clerk

Regular Meeting, Jan. 15, 1948

Ophthalmoscopy and Operations for the Reduction of High Blood Pressure. DR. ARTHUR J. BEDELL, Albany, N. Y.

This article was published in full in the November 1948 issue of the ARCHIVES, page 483.

DISCUSSION

Dr. W. Emory Burnett: It has been a great pleasure to hear Dr. Bedell and to consider certain additional criteria in the choice of patients for sympathectomy for relief of hypertension. As a surgeon, I am a little out of my depth in an ophthalmologic discussion, but I may discuss some of the considerations other than the eyegrounds in the selection of patients.

My associates and I have been watching carefully the results of the operation and comparing them with the prognoses. We have now approximately 60 cases in which we have done this operation. Some of them are too recent to permit proper evaluation.

We started out using the criteria which had been set up by the then known authorities in this work, particularly Peet and Smithwick; but none of them have been very reliable or accurate, and often there is great difficulty even in using them. Actually, the tests on which we have depended most in the past two years have been the production of a temporary sympathectomy, such as the use of tetraethylammonium bromide, or the chloride, and ascending spinal or ascending caudal anesthesia, effects which imitate those of the operation for a few minutes, the latter more accurately than the former, for the tetraethylammonium bromide produces a total sympathectomy for a few minutes and the spinal anesthesia is a selective or a partial one. So far, these agents have been the best means of forecasting results of sympathectomy that we have found. Although study of the eyegrounds has helped tremendously, one must realize that what is seen is the effect in a local situation, and this does not necessarily mean that the entire body will be similarly affected.

Another thing that may contribute to the inaccuracy of our correlation between results and forecasts is the fact that certain sympathectomies until recently have been rather limited, and a limited sympathectomy may not be sufficient to produce the desired effect, and thus does not actually disprove the accuracy of the forecast. The examination of the eyegrounds and other studies may indicate that a patient is a good prospect, and that he is likely to obtain benefit from sympathectomy. If the operation is too limited to interrupt all nerve connections with the splanchnic plexus, the procedure does not actually prove or disprove the point.

Because of this, we began, not quite two years ago, to do an extensive sympathectomy rather in the nature of the Grimson type, although he was doing complete lumbar removal as well. We have not done that but have used a transpleural approach, so as to get to the entire thoracic chain and easily approach the upper portion of the lumbar chain. We have almost routinely, not quite universally, removed ganglions from the second thoracic to the second lumbar, inclusive, thus leaving very little of the sympathetic chain still functioning. The immediate results of this more extensive operation are definitely better; and probably when we have followed the patients long enough to evaluate the late results, we may be able to say that the eyegrounds furnish much more accurate prognosis than we are now inclined to believe. The results of this more extensive sympathectomy have been much better, not only in the percentage of patients who have improved, but in the degree of improvement, so that we no longer have to be content with 10 mm. decrease

in diastolic pressure. We are rather disappointed if the patient does not show 30 mm. or better. There have been some failures in our series, despite the inclusion of spinal anesthesia and administration of tetraethylammonium bromide, but they have not been nearly so numerous as before.

DR. FREDERICK BOTHE: We surgeons have a long way to go to appreciate the finer points of study of the eyegrounds with which ophthalmologists are familiar. However, I wish to discuss a few points from that angle. All are familiar with the excellent results that Peet obtained in cases of malignant hypertensive vascular disease. In the early cases I was reluctant to do a sympathectomy once the condition was diagnosed as this disease. I did a sympathectomy in 2 cases at the request of the patients after I had told them I did not feel that such an operation would help them. The symptoms, particularly headache, were relieved in both instances, but otherwise they were not benefited. Others have experienced results comparable to mine in malignant cases. This variation in results could be explained on the ground that the criteria of changes in the eyegrounds denoting the beginning of malignant hypertensive vascular disease are variable in the minds of ophthalmologists.

Sympathectomy was performed in cases of essential hypertensive vascular disease to reduce the vasoconstriction. This constriction is either neurogenic or of humoral orgin. In the early sympathectomies only the splanchnic nerves were removed. As the results were studied, some surgeons felt that an improvement could be obtained if a more extensive sympathectomy was performed. Today various procedures are employed. Grimson performs a radical operation, in which he removes all the thoracic and lumbar ganglions, in addition to the splanchnic nerves and the celiac ganglion. Others are not so radical. The procedure Dr. Burnett just described is more radical than that which I use. At present my routine is composed of excision of the sympathetic cord from the tenth thoracic to the second lumbar ganglion, inclusive, and removal of the splanchic nerves and a piece of the celiac ganglion. It is to be hoped that future analyses of the results will decide whether the conservative or the more radical procedures give the best remote results. The improvement in the eyegrounds seems to be about the same with the various procedures.

In the past few years we have increased the scope of the use of sympathectomy. In the early work it was felt that a sympathectomy was not indicated if a patient had a history of a serious cardiovascular catastrophe. In view of the excellent results that Peet reported in cases of this type, I have tried the operation in a few such cases in the past several years. My patients had a history of either hemiplegia or coronary artery occlusion. These patients have been followed for two and a half to three years, and their improvement has justified the procedure in carefully selected cases.

A word as to the return of the hypertension. One should not forget that one is not in any way attempting to cure the hypertension. All one can hope to do is to produce a safety valve, in an effort to prevent or to postpone the cardiovascular catastrophies characteristic of this disease. Sympathectomy increases the capacity of the closed system through which the blood circulates. When the spasm again reduces it to

the preoperative capacity, the pressure returns, but it is hoped that the safety valve will persist. Results universally show that many patients have symptomatic relief even though the blood pressure returns to the preoperative level within three to six months after operation.

Dr. Glen G. Gibson: Dr. Bedell is better equipped than any other man in the world to bring this message to us, because of his extensive studies on over 2,000 cases of hypertensive vascular disease, which he has recently reported, and also because of his unexcelled photographic material on the fundus.

The surgery of hypertensive vascular disease has placed an additional burden on ophthalmologists in their diagnosis and classification of these vascular disturbances. When an ophthalmologist is called in consultation in a case of hypertension, he is asked to make a prognosis. That prognosis consists in two parts. The first part is how much damage has been done to the patient's vascular tree. The criterion for that is how much sclerosis is present.

Dr. Bedell has mentioned that the classification of sclerosis into four main types, as advocated by Wagner, is difficult and he objects to it on that basis. I agree with his objection that it is difficult to learn; in teaching residents, it is one of the most difficult tasks in the field of ophthalmology. However, once students of ophthalmology do learn this classification, they have a tool which is very useful. At least that has been my experience in the past fifteen years. The thing I was taught that has stood up best under clinical trial is the classification of hypertension into four grades of sclerosis, as taught me by Dr. Henry Wagner, who devotes most of his time to the classification of these vascular diseases. He believes thoroughly in this grading of sclerosis of the arterioles, and my colleagues and I have found it to be very useful in the study of these cases.

The second part of the prognosis concerns what the future course of the disease in this case under consideration is most likely to be. We feel we can estimate this to a certain extent by dividing cases of hypertensive disease into two groups: chronic, and a more active type. What are the ocular findings which differentiate these two different clinical types? In a case of chronic hypertensive disease, the most important sign is arteriovenous compression. I attach more significance to arteriovenous compressions than Dr. Bedell seemed to. The other sign which is most important in the chronic type is the color of the vessels. In the cases of early chronic hypertensive disease there is mild accentuation of the reflex stripe, and as the condition advances the change is that of the "copper wire" artery. The "silver wire" stage represents the more advanced degree of chronic sclerosis.

The changes associated with active hypertensive disease are, first, conspicuous attenuation; second, the presence of angiospasm and intermittent constrictions in caliber; third, the presence of edema in the retina with an arterial distribution, and, fourth, the presence of the various types of retinopathy, particularly edema of the disks. These signs are the signs of activity of the more fulminating types of hypertensive vascular disease.

Dr. Bedell has made some dogmatic statements and has some rather set ideas on which cases are suitable for surgery and which are not. My

data are much too incomplete, both as to number and as to duration, to permit any dogmatic selection of surgical cases. Therefore, what I have to say is to be taken as conjectural, and not as established. Analysis of our data suggests that the prognosis is best in cases in which there is grade 1 sclerosis. I am not sure this is a very significant statement, for the prognosis in cases of grade 1 sclerosis is better than that in cases of the severer grades of sclerosis.

The next trend indicated in my data is that the patients who show signs of activity of the disease, namely the vasospastic group, are the ones who show the most convincing evidence of improvement after sympathectomy. Conversely, patients with the more chronic form show less encouraging results. It is only fair, however, to point out that these are only trends, for there are instances of successful results in both groups; by and large, however, patients with the more active disease show the better response.

One of the main difficulties in this problem is to differentiate the retinopathy of acute vasospastic hypertensive disease and the retinopathy of malignant hypertensive vascular disease. One must admit that the classification of the serious forms of this disease is unsatisfactory, and Dr. Bedell implies he does not like the term malignant hypertensive disease. I am only too willing to agree with him that the classification is unsatisfactory as it stands. One of the important contributions of surgery in this field may be that the classification and understanding of hypertension will be on a higher plane than it was in the presurgical days. Early in the study of this condition, it was felt that the main benefit from operation was relief of symptoms, and that even though the blood pressure dropped temporarily that there was not much of permanent value to be had from the operation. It was believed in particular that malignant hypertensive disease was much too serious for surgical approach. Dr. Burnett has operated on a number of patients with the malignant form, and they show the best results. Dr. Bedell states that these patients should not be operated on, and on a logical basis I should be inclined to agree with him, but some of the patients who have had malignant hypertension have shown signs and symptoms of improvement. They have received benefits which could not be expected from the ordinary remissions which occur in this disease. The results of Dr. Burnett's surgical work have changed my opinion of this problem from one of complete disbelief in the value of the procedure to one of cautious enthusiasm. The postoperative findings in the fundus are unpredictable, but are sometimes dramatic.

I hope Dr. Bedell will favor us with one of his usual very effective rebuttals. I rank him as "No. 1 rebuttalist in ophthalmologic circles"; so I think you gentlemen are in for a treat.

Dr. Arthur J. Bedell, Albany, N. Y.: Dr. Burnett, you have given us the benefits of your mature deliberations. I was told before I came to Philadelphia that the address of a guest was not discussed, and I asked that the habit be broken. How fortunate that the rule was laid aside. You were gracious to come and tell us about your long experience in the surgical treatment of hypertensive disease.

You, Dr. Burnett, have added much to knowledge of this condition. I have, of course, read the literature, and as a result have been left in a state of confusion. The reports from the various clinics have shown

that some surgeons go high in the thoracic region and some low in the lumbar region, and all have claimed good results. I have felt, therefore, that perhaps it was skill of the operator, rather than the extent of the operation, that led to the favorable outcome. I did not tell the ophthalmologists here the details of the operations, for I felt that if they were sufficiently interested they would read about them. You, however, have saved them the effort, and I am sure they are grateful to you for the clear exposition of the nature of the present operation.

Dr. Bothe, you have added much to the value of the exposition. You have helped us understand some of the problems you encounter and overcome. You have referred to Peet's summaries. In his last report, I believe, he reported 1,500 operations. From an ophthalmologic standpoint, and of course that is all I am discussing, his citations are incomplete. He has done things that I would not wish to have done to me. He has drawn some conclusions at variance with those of other surgeons. Your statement regarding hemiplegia has been of great interest, for your good results are surprising. They cause us to pause, and in the future to be more cautious in excluding cases of this type from the possible benefits of operation.

Dr. Gibson, you have added much to the value of the paper, for you have amplified and clarified many of the points which I have touched upon and have brought into relief questions in which there is a difference of opinion. Your stand has been made so clear that I am sure we all recognize your extensive experience and the value of your deductions. I thoroughly appreciate your delightful discussion and feel that it has been most profitable to all who have heard it.

Perce DeLong, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Regular Meeting, Feb. 19, 1948

Laurence-Moon-Biedl Syndrome: Presentation of a Case. Dr. O. A. Capriotti (by invitation).

A brief review of the literature was presented, followed by presentation of a case.

REPORT OF CASE

A woman aged 20 was admitted to the Wills Hospital in December 1947, to the service of Dr. James S. Shipman, with the chief complaint of poor vision. The patient stated that she had begun to have difficulty with her vision at about 12 years of age. Her vision decreased rather rapidly in the next few years, necessitating her stopping school. Since the age of 16 her vision had become so poor that she was unable to see objects and had to learn to feel her way around the house. She has always been obese, even in infancy. There had been six fingers on each hand, the extra fingers having been removed when she was an infant.

Family History.—The patient was the third of 12 siblings. In addition, her mother had had 6 miscarriages. Two children died during infancy. Four brothers and 5 sisters were living. One sister, aged 15, the sixth sibling, was blind and obese. Another sister, aged 9, the eighth sibling, was blind and obese and had heart disease. The youngest

child, aged 1 year, was fat. The paternal grandmother was being treated for a tumor of the right eye.

Physical Examination.—The patient was 56 inches (142 cm.) in height and weighed 135 pounds (61.2 Kg.). She was obese, with the fat distributed over the arms, breasts, abdomen and thighs. The right breast was about twice the size of the left breast. The hair distribution under the arms and over the mons veneris was normal but rather sparse. Her hands and feet were short and stubby. She had genu valgum (knock-knee) and congenital clubfoot (talipes valgus). There were scars over the ulnar aspect, near the distal portion of the fifth metacarpal bone, of each hand where the supranumerary digit was removed.

A blowing systolic murmur was heard over the apex.

Gynecologic Examination.—The labia minora were about one-third normal size; the clitoris was very small and the uterus was infantile, as determined by rectal examination.

Neurologic Examination.—The mental age was 10 years; the intelligence quotient was 67 as determined by the Hayes-Binet test. General neurologic examination revealed an essentially normal condition except for impairment of motor power.

Roentgenographic Examination.—The skull was rather small, but was otherwise normal. The sella turcica was normal. Roentgenograms of the arms and hands showed bowing of both radiuses; the metacarpal bones were small, and the second phalanges were short and stubby. The legs and feet showed a congenital type of clubfoot (talipes valgus), with short and stubby metatarsal bones and second phalanges.

Laboratory Studies.—The Wassermann and Kahn reactions of the blood were negative. The basal metabolic rate was + 2.5 per cent. The glucose tolerance test indicated mild diabetes insipidus. The blood count and the urine were normal.

Ophthalmologic Examination.—Vision was reduced to light perception and projection in each eye. The visual fields of both eyes showed a marked concentric contraction, the field of the right eye being contracted to about 7 degrees, and that of the left to 15 degrees, with a 10 mm. target at a distance of 33 cm., and the finger used for fixation.

External Examination revealed an essentially normal status except for horizontal nystagmus. The pupils were equal and round and reacted equally to direct and consensual stimulation.

Ophthalmoscopic Examination.—Right Eye: The lens showed fine posterior polar opacities. Fine granular opacities were present in the vitreous. A large, well defined area of pigment lay on the temporal side of the disk, which was waxy in color, with a deep physiologic cup. There was about 6 D. of myopia. The arteries were narrow, being about one-third the normal size. The arteriovenous ratio was 2:3. The macula was poorly defined and granular in appearance. The retina was thin; the choroidal vessels were easily seen. About 2 disk diameters away from the disk were punctate deposits of pigment. On their course to the periphery these became linear and more diffuse. They were not particularly perivascular. Some of these may be described as of "bone corpuscle" type.

Left Eye: The picture was essentially the same as that in the right eye.

In Summary, the case presented demonstrated the classic features of the Laurence-Moon-Biedl syndrome, namely, pigmentary degeneration of the retina, the Frölich type of obesity, hypogenital dystrophy, polydactyly, mental retardation and familial occurrence. In addition, the patient had the skeletal defects of genu valgum, talipes valgus, short metacarpal bones and short second phalanges of the hands and feet.

DISCUSSION

Dr. James S. Shipman: Few of us have often seen cases of this type. I did not make the diagnosis, and I do not know who made the original diagnosis. One of the residents asked me to see the patient and told me the diagnosis before I saw her. However, if one has ever seen a case of this syndrome he should not miss the diagnosis.

We all have seen many cases of retinitis pigmentosa, and this case, on examination of the eyes, is a typical instance of this condition. In addition, the other signs and findings which Dr. Capriotti has so well described are present.

It would appear from the literature that it is rare to find such a classic form and distribution of retinal pigment in this syndrome. According to Clay, it occurs in only 15 per cent of the cases that have been reported. For this reason, I feel that this case is a typical instance of retinitis pigmentosa, with practically all the other symptoms and signs of the Laurence-Moon-Biedl-Bardet syndrome. I am sorry that the pictures which Dr. Capriotti obtained do not show the true condition of this patient's fundi, for the fundi do show typical retinal pigment on top of the vessels with the characteristic bone corpuscle-like arrangement.

This case also makes us think about the cause of retinitis pigmentosa. No one has ever given a satisfactory explanation of this condition. Many theories have been advanced. Probably the most recognized one is that of "abiotrophy," premature senility, advanced by Collins in 1922, when he talked on this subject in Washington, D. C. Verhoeff is one of the few men who made microscopic section of an eye with retinitis pigmentosa, and he is inclined to give considerable credit to this theory of abiotrophy. He also feels that there is a progressive degeneration of the retinal neuroepithelium with migration of pigment. He does not believe that the vascular theory, with sclerosis of the choroid, is well borne out by microscopic findings.

Other theories that have been advanced are that of "hepatic disease" with liver dysfunction, as found in some cases by Takahashi, as well as that of sex hormone and vitamin A deficiencies. Still another theory toward which this case points is that of a disturbance of the endocrine glands, perhaps of the pituitary. Certainly, this case would make one think of the possibility of the endocrine glands playing a causative role in retinitis pigmentosa.

Dr. Francis Heed Adler: Up to a few years ago most authors regarded this syndrome as a typical pigmentary degeneration of the retina with signs and symptoms of pituitary dysfunction; then Lyle presented a paper which seemed to me to challenge this concept. He pointed out that the onset is nearly always with a central scotoma and

loss of central vision, which is certainly not characteristic of pigmentary degeneration, and the case reported bears this out. My feelings now is that less is known about the disease than was thought a few years ago.

DR. I. S. TASSMAN: About ten or twelve years ago I observed three members of one family who had this condition. They presented the classic form, almost identical with that so well presented here.

In a classic case of the Laurence-Moon-Biedl syndrome, pigmentary degeneration of the retina is nearly always typical in its appearance, and is one of the cardinal signs. The other cardinal clinical signs are lowered mentality, obesity of the Frölich type, hypogenitalism and sometimes polydactyly. The patient is usually short in stature and has spade-shaped hands, often with deformity of the metacarpal, metatarsal and phalangeal bones. This condition is easily recognized. I agree with Dr. Shipman that dysfunction of the pituitary gland may be present in cases of this syndrome. The defect exists before birth and results in impairment of the tissues during the course of development. On the other hand, in arachnodactyly there is bilateral ectopia lentis associated with an overgrowth of the long bones, resulting in gigantism. This suggests the possibility of hyperpituitarism in these cases.

DR. P. ROBB MCDONALD: Several years ago, while working in Dr. Adler's department at the University, I was also interested in the endocrine aspect of this disease. At that time, Dax, in England, had just published a paper on the hormones of the pituitary gland, and had tried the diagnostic test in cases of retinitis pigmentosa.

We attempted to confirm that work and did three types of experiments. We injected hormones into hypophysectomized frogs in an attempt to see whether the melanophore-expanding hormone had any effect on the frog's pigment. We took the same hormone, using many times the normal dose, and injected it into gray rats in an attempt to produce disturbances in pigment; that likewise was negative. Finally, we obtained blood from about 87 patients, and injected this into hypophysectomized frogs as a method for testing the hormone. In using hypophysectomized frogs, the test was entirely negative, and we concluded that there was at least no relation between the melanophore-expanding hormone of the pituitary gland and dispersion of pigment in the retina.

Inheritance of Arachnodactyly, Ectopia Lentis and Other Congenital Anomalies (Marfan's Syndrome) in the E. Family. DR. FRANK C. LUTMAN (by invitation) and DR. JAMES V. NEEL (by invitation). Ann Arbor, Mich.

This paper was published in full in the March 1949 issue of the ARCHIVES, page 276.

DISCUSSION

DR. JAMES S. SHIPMAN: I should like to ask Dr. Lutman how many of the patients whom he has studied had retinal detachment. Two of the last 5 patients with this condition whom I saw had bilateral retinal detachment.

DR. FRANK C. LUTMAN: None of the members of the family had retinal detachments. However, the last 6 persons with the Marfan syndrome whom I have seen were not related to this family, have had some ocular surgery, and two of them had detachments.

Ophthalmic Research for the Improvement of Fluoroscopic X-Ray Screens. ROBERT H. PECKHAM, PH.D.

X-ray screens have been greatly improved since they were first discovered, but further improvement requires ophthalmic, rather than chemical or physical, research. This is because the screens must be modified from rod stimulus screens to cone stimulus screens. The new cone stimulus screens must be selected according to their retinal effect, in terms of color, brightness, resolving power and after-glow. Such new screens have been studied in this manner in the department of ophthalmology of Temple University Medical School, and my associates and I have been able to select new and improved screens from those prepared for these experiments by the United States Radium Corporation. These screens are being currently tried in the department of radiology of Temple Hospital.

The development of new technics of accurately measuring visual response to these screens can be expected to yield new data on retinal physiology, in a form which may be applied to improve ophthalmic practice.

DR. GLEN G. GIBSON: Dr. Peckham has been unnecessarily modest in his presentation this evening, and the truth of what he has accomplished can best be learned from discussing this problem with Dr. Chamberlin, who is using the new screens. He states that the new screens have had a definite advantage to them in the field of fluoroscopic diagnosis, and he is enthusiastic about them, because they have helped him so much in a field which previously has left much to be desired. In order that one may understand what has been achieved, it is necessary to point out that one of the commercial companies who previously were making these screens had a monopoly for many years, and this monopoly, like so many of those things, was based on unsound physiologic optics. As a result of this monopoly, no definite progress has been made in this field for many years. Dr. Peckham's contribution is such that this monopoly has now been broken, and commercial companies are doing a number of things to help improve this subject. Dr. Peckham's work is not necessarily revolutional, but it is evolutional; he has made real progress, and I anticipate that he will make even more as he carries on his studies.

Subzygomatic Decompression for Exophthalmos of Cranial Stenosis. DR. EDMUND B. SPAETH.

A case presented with a moving picture film (in color) illustrated severe bilateral exophthalmos with craniostenosis. Exophthalmos was so severe that surgical relief was necessary. The deformity of the orbit was so severe, also, that transfrontal orbital decompression through the roof of the orbit seemed to offer little, if any relief. Subzygomatic decompressions were therefore done. There was a recession in the exophthalmos on the right of slightly less than 1 cm., and on the left of 4 mm. The left orbit was the shallower of the two, although the exophthalmos on that side was no more marked.

Since the operation the patient has been wholly comfortable, and there has been no recurrence of the spontaneous prolapse of the eyeball in front of the lids, a condition which had been distressingly recurrent prior to introduction of operative procedure.

CASE HISTORY NO. B106-31

Name: [redacted]*
Occupation: Comptometer Operator

First Rx

Sept. 10 -- Hyperope. Patient wore white lenses in the following correction:

O.D. +.25 ○ +1.75 ax 90
O.S. +.25 ○ +2.25 ax 80

Sept. 18 -- Patient comfortable. Correction satisfactory.

Nov. 15 -- Patient returned reporting visual distress. Discussion revealed fluorescent lights were installed in office concurrent with complaint of headaches and fatigue. Patient noticeably critical and difficult. New refraction, including light tolerance test. Soft-Lite Lenses in the same correction:

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O.D. +.25 ○ +1.75 ax 90
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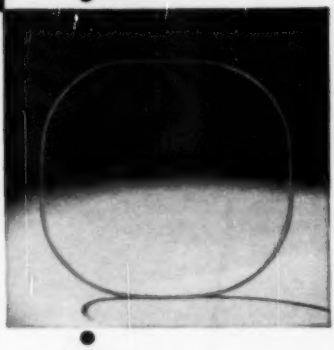

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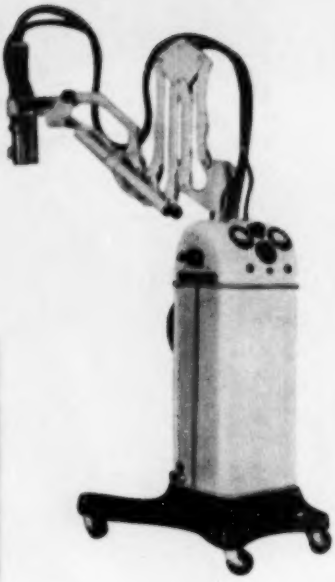

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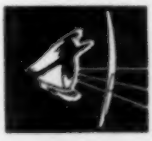

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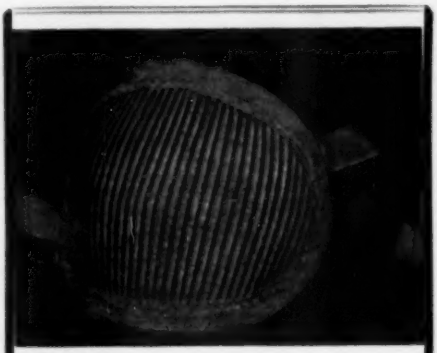

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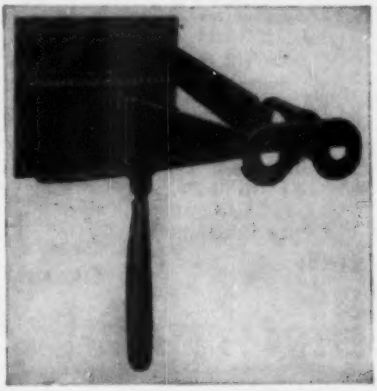

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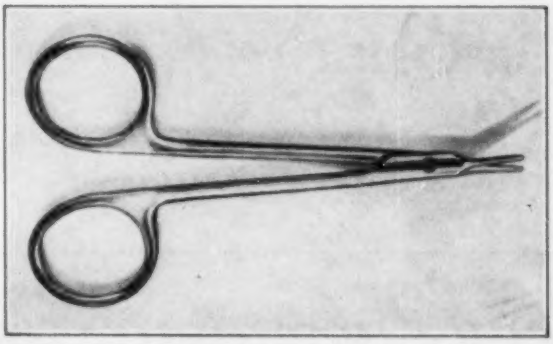

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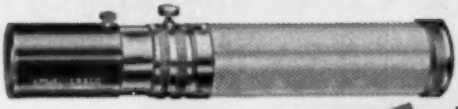

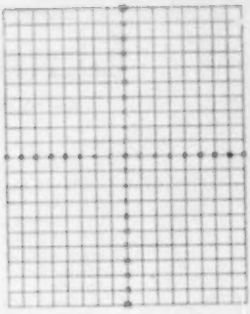

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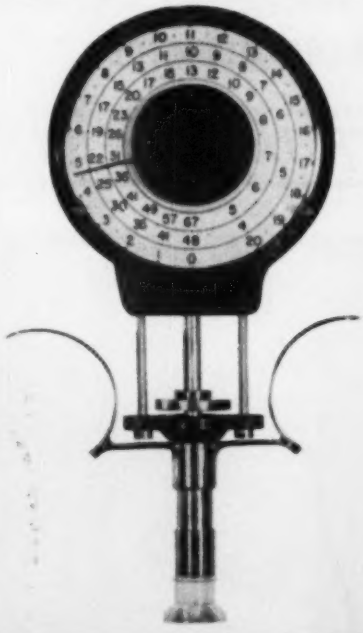

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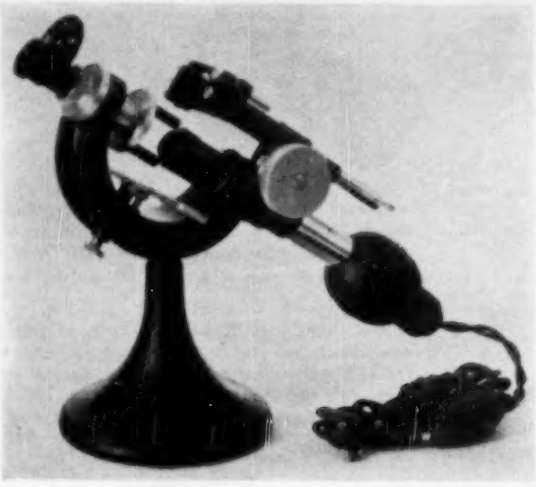

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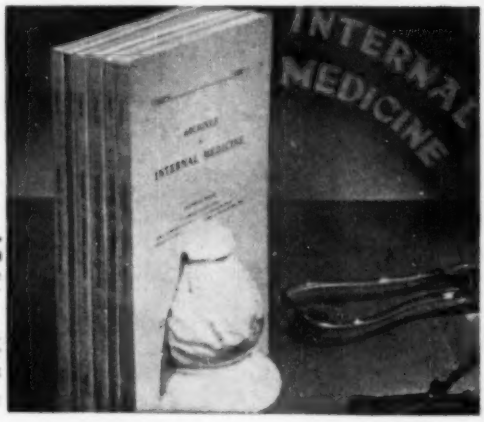

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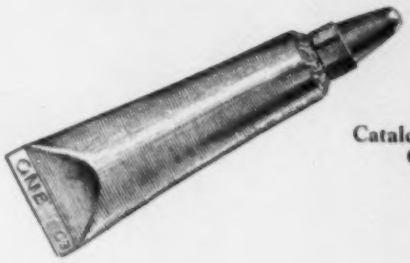

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